DOES NOT CIRCULATE
UNIVERSITY
OF MICHIGAN
SEP 30 1955
MEDICAL

A.M.A. Archives OF SURGERY

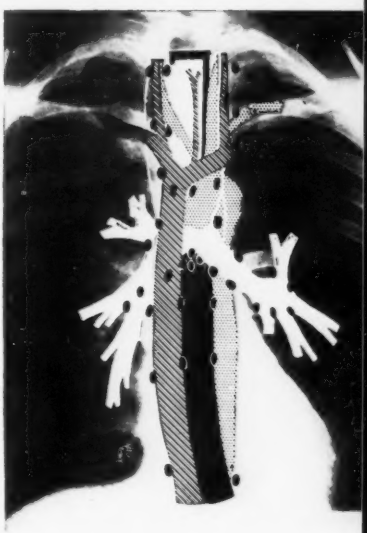
THE PHYSICIAN'S ALTER EGO — LEON J. LEAHY, M.D.
A SIMPLIFIED AND RAPID ANATOMICAL APPROACH TO PAROTIDECTOMY — E. S. BRINTNALL, M.D., ET AL.
BILATERAL SIALOANGIECTASIS OF PAROTID GLANDS — J. DEWEY BISGARD, M.D., ET AL.
AN EVALUATION OF NEWER METHODS IN THE DIAGNOSIS OF HYPERPARATHYROIDISM — B. E. BRUSH, M.D., ET AL.
MEDIASTINAL TUMORS OF THYROID ORIGIN — J. L. EHRENHAFT, M.D., ET AL.
THE SURGICAL TREATMENT OF RETROTRACHEAL INTRATHORACIC GOITER — ELMER R. MAURER, M.D.
THYROID CANCER IN A GENERAL HOSPITAL — DANIEL T. CLOUD, M.D., ET AL.
ISOTOPE TECHNIQUES FOR MEDIASTINAL TUMORS — ROBERT D. SWEDENBURG, M.D., ET AL.
EXPLORATORY THORACOTOMY IN CHRONIC LYMPHADENITIS OF THE MEDIASTINUM — THOMAS R. LEECH, M.D., ET AL.
THE INFLUENCE OF STRESS UPON LIVER FUNCTION IN OBSTRUCTIVE JAUNDICE — CHARLES A. MACGREGOR, M.D., ET AL.
A BACTERIOLOGIC STUDY OF PORTAL-VEIN BLOOD IN MAN — WILLIAM E. SCHATTEN, M.D., ET AL.
THE HAZARDS OF SURGERY IN IRRADIATED TISSUE — DAVID W. ROBINSON, M.D.
FIXATION OF SKIN FLAPS IN RADICAL MASTECTOMY BY SUBCUTANEOUS SUTURES — BERNARD B. LARSEN, M.D., ET AL.
THE EXPOSURE METHOD OF BURN TREATMENT — CARLYLE E. WILSON, M.D., ET AL.
EXPERIMENTAL EVALUATION OF PROLONGED HYPOTHERMIA — BERNARD FISHER, M.D., ET AL.
PLIABLE PLASTIC AORTIC GRAFTS — EDMUND J. HARRIS, M.D., ET AL.
PERIPHERAL ARTERIOSCLEROTIC VASCULAR DISEASE IN DIABETICS — ROBERT E. L. BERRY, M.D., ET AL.
SPRING VALVE FOR MITRAL INSUFFICIENCY — PRESCOTT JORDAN JR., M.D., ET AL.

COMPLETE CONTENTS ON FIRST PAGE

SEPTEMBER 1955

VOLUME 71 NUMBER

From Leech et al., p. 383.



AMERICAN MEDICAL ASSOCIATION Publication

For the smaller hospital—an "enormous advance"[1]

A vital aid in reducing surgical risk is now at the disposal of every hospital, large and small. Blood volume studies by the Evans Blue technic require neither elaborate facilities nor highly trained specialists. The notion that only major institutions can run the test "is a completely false assumption," according to experience in a small Southern hospital.[1]

"Readily mastered by the average technician,"[2] the Evans Blue technic permits a far more reliable evaluation of actual blood deficits than is possible with older methods.[3,4] Blood transfusions can be given exactly when needed, and in the exact amounts needed.

The range of surgery has thus been vastly extended. Procedures which once seemed daring can now be performed — even in older patients—with less fear of surgical or postoperative shock.[1,3]

1. Parsons, W. H., et al.: *Ann. Surg.* 135:791 *(June) 1952. 2. Whiting, J. A., and Hotz, R.: Surg., Gynec. & Obst.* 97:709 *(Dec.) 1953. 3. Beling, C. A.,* et al.: *Geriatrics* 7:179 *(May-June) 1952. 4. Barbour, C. M., Jr., and Tennant, R.: J. Urol.* 71:497 *(April) 1954.*

Evans Blue

(T-1824)

WARNER-CHILCOTT

5.0 cc. ampuls—No weighing or calibration required. Available at leading laboratory supply houses. Literature sent on request.

TABLE OF CONTENTS

VOLUME 71 SEPTEMBER 1955 NUMBER 3

ORIGINAL ARTICLES

Papers Read at Twelfth Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955

PAGE

The Physician's Alter Ego
Leon J. Leahy, M.D., Buffalo 307

A Simplified and Rapid Anatomical Approach to Parotidectomy
E. S. Brintnall, M.D.; R. T. Tidrick, M.D., and W. C. Huffman, M.D., Iowa City 331

Bilateral Sialoangiectasis of Parotid Glands
J. Dewey Bisgard, M.D., and Kenneth Kimball, M.D., Omaha 337

An Evaluation of Newer Methods in the Diagnosis of Hyperparathyroidism
B. E. Brush, M.D.; W. E. Chase, M.D., and M. A. Block, M.D., Detroit 342

Mediastinal Tumors of Thyroid Origin
J. L. Ehrenhaft, M.D., and Joseph A. Buckwalter, M.D., Iowa City 347

The Surgical Treatment of Retrotracheal Intrathoracic Goiter
Elmer R. Maurer, M.D., Cincinnati 357

Thyroid Cancer in a General Hospital
Daniel T. Cloud, M.D., and Charles D. Branch, M.D., Peoria, Ill. 366

Isotope Techniques for Mediastinal Tumors
Robert D. Swedenburg, M.D.; William M. Tuttle, M.D., and K. E. Corrigan, Ph.D., Detroit 372

Exploratory Thoracotomy in Chronic Lymphadenitis of the Mediastinum
Thomas R. Leech, M.D.; Charles V. Meckstroth, M.D., and Karl P. Klassen, M.D., Columbus, Ohio 383

The Influence of Stress upon Liver Function in Obstructive Jaundice
Charles A. Macgregor, M.D.; Joseph B. Griffith, M.D., and Gordon A. Munro, M.D., Denver 395

A Bacteriologic Study of Portal-Vein Blood in Man
William E. Schatten, M.D.; John D. Desprez, M.D., and William D. Holden, M.D., Cleveland 404

The Hazards of Surgery in Irradiated Tissue
David W. Robinson, M.D., Kansas City, Kan. 410

Fixation of Skin Flaps in Radical Mastectomy by Subcutaneous Sutures
Bernard B. Larsen, M.D., and Charles Hugan Jr., M.D., Cleveland 419

The Exposure Method of Burn Treatment
Carlyle E. Wilson, M.D.; Kenneth F. Kimball, M.D., and Samuel A. Swenson Jr., M.D., Omaha ... 424

Experimental Evaluation of Prolonged Hypothermia
Bernard Fisher, M.D.; Clem Russ, Ph.D.; Edward Fedor, Ph.D.; Ralph Wilde, M.D.; Perry Engstrom, M.D.; John Happel, M.D., and Paul Prendergast, B.S., Pittsburgh 431

Pliable Plastic Aortic Grafts
Edmund J. Harris, M.D.; Harris B. Shumacker Jr., M.D.; Harry Siderys, M.D.; Thomas C. Moore, M.D., and Paul F. Grice, M.D., Indianapolis 449

Peripheral Arteriosclerotic Vascular Disease in Diabetics
Robert E. L. Berry, M.D., and C. Thomas Flotte, M.D., Ann Arbor, Mich. 460

Spring Valve for Mitral Insufficiency
Prescott Jordan Jr., M.D., and James Wible, M.D., Detroit 468

A. M. A. ARCHIVES OF SURGERY

VOLUME 71 SEPTEMBER 1955 NUMBER 3

COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

WALTMAN WALTERS, Chairman, Rochester, Minn.

LESTER R. DRAGSTEDT, Chicago

ROBERT ELMAN, St. Louis
ALTON OCHSNER, New Orleans
ARTHUR W. ALLEN, Boston
ALFRED BLALOCK, Baltimore
FRANK HINMAN Jr., San Francisco
G. E. LINDSKOG, New Haven, Conn.
BARNES WOODHALL, Durham, N. C.
WALTER MADDOCK, M.D., Chicago

HENRY KING RANSOM, M.D., Ann Arbor, Mich.

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. American Journal of Diseases of Children. Robert Barrett Lawson, M.D., Chief Editor, 1000 N.W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12:50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

Check, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

A.M.A. Archives OF SURGERY

The Physician's Alter Ego

LEON J. LEAHY, M.D., Buffalo

In my selection of a subject for this Presidential Address, I must confess to the influence of a long-standing interest concerning the outstanding achievements of physicians in nonmedical pursuits. Also, I thought a respite from scientific papers might be welcome.

I had thought too, that my choice had some originality but I was quickly disillusioned of this idea on visiting the reference libraries. Various aspects of the subject I planned to cover had been dealt with in numerous articles and books. This fact somewhat discouraged me and I entertained the idea of discussing a clinical matter but found myself reverting to my original intention. The predicament seemed similar to that of the Australian who wished to purchase a new boomerang but went crazy trying to rid himself of the old one. I have proceeded, however, in the hope that my efforts might provide some consolidation of the widely dispersed information.

Having set the stage, now let us meet the cast of "Medical Truants." This was the title used by Sir Berkley Moynihan in his Linacre Lecture at Cambridge. We shall find many degrees involved. The nonmedical accomplishments have often represented hobbies only. In many instances, however, these activities have displaced medicine as careers.

We shall seldom find men of great prominence in both medicine and a nonmedical pursuit. Those famous in medicine are more often only mediocre in another field, and those who achieve eminence in other fields usually either abandon our profession or at least leave no mark of note in it.

I feel certain many names worthy of mention have been omitted; some of these are inadvertent, others deliberate in the interest of space. I am reminded of the advice an old preacher gave to a young man who was just undergoing instruction, to the effect that, "There were no souls saved after the first twenty minutes."

Imhotep (circa 3150 B. C.) was the first physician known in history and is so ancient that he is practically a legend. He lived during the Third Dynasty and the fact has been proved that he was a real God of Medicine, not a mythical character like Aesculapius. His great contributions to Egyptian medicine made the people worship him as the God of Knowledge. He existed before Cheops and the later pyramids by approximately a thousand years and built the step pyramid at Sakkara which is the oldest within our knowledge. It might be said that Imhotep achieved greater fame as an architect than a physician. His name has gone down in history as one of the greatest men of that era. He became a God of Medicine and was invested with the attributes of a diety. Figures and statues

Submitted for publication April 25, 1955.

Clinical Professor of Surgery, University of Buffalo School of Medicine.

Presidential Address, given at the Twelfth Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

Since this article represents a wide departure from the type of article usually published in the Archives, it is printed as it was received from the author, to preserve intact the spirit of the delivered address.

memorialized him and with Amenophis, stands alone as the only beatified mortals in Egyptian history.

ACTORS

This art has shown a relative scarcity of doctors among its prominent members, at least my efforts have failed to discover many of significance.

Sir Charles Wyndham (1837-1919) a prominent English actor who received his medical education at the College of Surgeons and Kings Hospital in London, studied in Dublin also. It would appear as if he promptly took to the stage since he performed in London at the age of 25. Following this, he left for America and became Brigade Surgeon with the Federal Army during the Civil War. This career was also abandoned for the footlights and he joined John Wilkes Booth in New York City. Great success followed this and he appeared in London with many great actors and actresses. Subsequently he became a prominent producer and theatre owner before his death.

James Sheridan Knowles (1784-1862) was an Irish dramatist and actor who served in the militia but left the service to study medicine. He did not enter practice but forsook that profession for the stage. His financial success was not commensurate with the fame he enjoyed as a playwright and actor, so he taught school as a source of income. His greatest success was the *Hunch Back* and he eventually became a Baptist preacher to wind up a varied career.

ART

Although there are in all probability more physicians indulging in this medium as an outlet for their cultural instincts than in any other field, it was extremely difficult for me to discover a large number of names that have made lasting contributions. There are many prominent members of our profession who have achieved very artistic and pleasing results which display great ability but only a few are remembered for these rather than their medical accomplishments.

Offhand, I can recall four individuals who are or have been members of this Society and have had their paintings exhibited. Namely, Dr. Fred Coller, Dr. Michael Mason, Dr. John Hartzell and the late Dr. Fraser B. Gurd. The many exhibits which are held of contributions from medical men in the field of art always show extreme talent and many of the articles rank with professional efforts of great quality. Our confrères have from time immortal always shown a great interest in art; this perhaps came down from the early anatomical illustrations, some of which are masterpieces. It has been used, like music, as a form of therapy. There are many collectors in our group.

Leonardo DaVinci (1425-1519). When speaking of DaVinci, one feels no restraint in the use of superlatives. To mention a few of the descriptive comments, I encountered, let me quote as follows: "One of the greatest minds of the Renaissance," "Perhaps the most richly gifted by nature amongst all the sons of man," and "The greatest individual within our knowledge." His medical success is overshadowed by the other accomplishments he achieved but they deserve recognition on their own merit, since he enjoyed the honor of being acclaimed as the greatest physician of the 15th century. He was a great anatomist and physiologist, acquired an extensive knowledge of the circulation before Harvey's publication and was the first to describe arteriosclerosis. He was presumably the natural son of a prominent and prosperous Florentine lawyer, being brought up as a member of the family. Other accomplishments endowed upon this most extraordinary individual include success in mathematics, sculpturing, inventing, philosophy, poetry and an amazing range of other fields. The contributions made by DaVinci to the world of art are legend. As the creator of the most famous portrait in the world, *Mona Lisa*, he achieved immortal fame. In most opinions its charm and beauty have never been equalled, which well rewarded him for the six years spent perfecting it. Five of his paintings were on the list of those to be

saved first, in case an emergency existed at the Louvre. Those did not include The Last Supper, which hangs in Milan, and is thought by many to be the greatest painting ever made. He was the master of Michaelangelo and Raphael according to the opinion expressed by Cellini.

Seymour Hayden (1818-1910) obtained his medical education in England and France. He was a very successful practitioner who not only became a member of the Royal College of Surgeons at the age of twenty-four but also was Vice-President of the London Obstetrical Society. He was the personal physician for William Thackery and attended him during his final illness. Hayden was also an accomplished musician and composer, but his lasting fame resulted from the great ability he possessed as an etcher. He was the founder of the Royal Society of Painters, Etchers and Engravers for which Queen Victoria bestowed a knighthood upon him in 1894. His wife was the half sister of James McNeil Whistler but according to reports, the two artists violently disagreed on many things. Hayden is credited with the popularization and revival of etching. Those who appreciate this form of art will agree that his ability and fame rate him as one of the foremost exponents.

Pieter Camper (1722-1789) was a graduate in both medicine and philosophy from Leyden and became a professor at three separate Dutch Universities. He was a great anatomist, combining this science with art for illustrative purposes. Like Hayden he broke away from this tradition and chose classical subjects. His versatility led him to use many media since he worked in oils, India ink, charcoal, pastels, etching, mezzotints and sculpturing. Most of his fame arose from the excellence of his anatomic illustrations.

Tait McKenzie, a Canadian surgeon who graduated from McGill in 1891, is considered as one of the very important doctor-artists. He has been referred to as a sculptor of worldwide fame. McKenzie, like many others, was an anatomist and since he also was interested in athletics, his work showed somewhat a revival of the Greek influence. He also worked with water color and charcoal and was the artist for two war memorials in Edinburgh.

Sir Frederick Grant Banting (1891-1941) the great Canadian physician, became a very active painter with considerable natural ability. He never took formal lessons but went on many sketching trips, even to the Arctic with A. J. Jackson, who advised and criticised him. Although his immortality results from scientific rather than classical contributions, the work he created was well received, far above average and merited a book being written on the subject.

Alexander Anderson was born in New York City and was the son of a printer. At the age of twelve he had his own plates made after having read about it in the Encyclopedia and began business himself. In view of the fact that he was doing a large amount of copying medical illustrations, his father decided he should study medicine; so the young man paid his own expenses in this manner. He graduated from Columbia in 1796. Three years prior to this, he used wood and after overcoming early difficulties with this medium, he eventually employed it exclusively and instructed pupils in its use. Although a good minature painter, Dr. Anderson is also known as the first wood engraver in America.

BOTANISTS AND GEOLOGISTS

Many older physicians exhibited a deep interest in botany and contributed greatly to the development of this science. The close relationship between materia medica and plants undoubtedly encouraged this interest. This was the favorite type of therapy from the time of Galen for over a thousand years until Paracelsus at the beginning of the Renaissance worked to popularize the use of minerals and metals in preference to vegetable materials.

Georg Agricola (1490-1555), the latter name is the Latin form of Bauer, which was his real surname. Dr. Agricola was born in Saxony but received his medical degree in Italy and practiced in the center of the

mining and smelting industry in Germany. His interests although chiefly metallurgical in nature, included industrial medicine, theology, mathematics and history. He is known as the Father of Minerology but was a pioneer in physical geology and the first to classify minerals in a scientific manner. His many published works on the above subjects received great recognition. President and Mrs. Hoover translated his celebrated "De re metallica" into English in 1912.

Carolus von Linne (Linnaeus) (1707-1778) was the Father of Scientific Botany. He graduated in medicine from Harderwijk, settled down to practice in Stockholm after writing many books, lecturing and traveling extensively. He was Professor of Medicine at Upsala but transferred to the Chair in Botany after one year. The method of nomenclature introduced by him called the binominal system has been used extensively since. This created a new concept in the science and included the principles of both genera and species in the names. He also was one of the earliest contributors to the science of crystallography.

Alexander Garden (1728-1791) graduated from medical college in Scotland, practiced in South Carolina with great financial, social and professional success. His interest in botany was great since he wrote and spoke extensively on the subject. Frequently he exchanged ideas with Linnaeus, who was responsible for his membership in the Royal Society of Upsala. John Ellis, a great English naturalist, named the flower gardenia for him.

Leonhardt Fuchs (1501-1566), called the Botanist of the Renaissance, was born in Bavaria, studied at Ingolstardt and received the degree Doctor of Medicine from that institution. Dr. Fuchs was Professor of Medicine at Tübingen but wrote many books on plants which were collected and published in 1566. Fuschia was named for him; although originally only a plant, it is now also a color.

An article entitled, "Medicine, Mother of Sciences" lists over sixty-six members of our profession who were early geologists and left memorable contributions behind them.

James Hutton (1726-1797) was born in Edinburgh and received his qualifications as a Doctor of Medicine after studying in that city and Paris. His activities were those of farming, rather than medicine, but he devoted the last thirty years of his life to a scientific geological study. His investigation of the origin of the earth worked back from the minerals and rocks. This was a novel approach, since mineralogy existed as a science but geology did not. His notions of erosions and upheavals on the earth's surface were original as were his theories concerning the atmosphere. He is credited with the creation of the first geological maps.

Erasmus Darwin (1731-1802) was the grandfather of the famous Charles Darwin, the noted naturalist of evolutionary fame who was poet, great botanist and wrote *The Origin of the Species*. Charles did not finish his medical education, but Erasmus practiced in Nottingham. He was himself a botanist and poet whose work served to inspire his grandson's great work.

William Henry Fitton (1780-1861) was born in Dublin, educated at Trinity College and Edinburgh University. Fitton practiced actively in Northhampton but abandoned medicine for geology, as he held degrees in both sciences. His observations of the strata and chalk formations were original, and the publications made by him were extremely important. He was elected as a Fellow to the Royal Society and President of the London Geological Society, which group awarded him their medal.

EXPLORERS

Medical men have in the past assumed a very prominent position in the discovery and exploration of unknown lands. Although there are lengthy articles giving many names of important discoveries by physicians, I will mention but a few.

Toscanelli (1397-1482) was a prominent medical practitioner and astronomer in Florence who not only greatly inspired but also

directed Columbus in his search for the New World. His map was used as a chart on the voyage. A second physician, Garcia Fernandez, later gave additional council and encouragement to the plan, but it was Toscanelli's direction to go westward that led him to his destination. Two surgeons accompanied him on the voyage, rendering great assistance. Maestre Alonzo was aboard the Santa Maria and Maestre Juan aboard the Pinta. The latter acquired the questionable honor of being the first member of our profession to be massacred by the Indians.

Mungo Park (1771-1806) graduated from the University of Edinburgh, then went to London where he took a position as ships surgeon and spent a year sailing to Sumatra. Following his return, he went to Africa on an exploration of the Niger River area, then married and became a practitioner upon return. This latter career was short-lived and he returned to Africa in charge of an expedition which lost 90% of its European members. Park continued but met his end in a battle with the natives after overcoming the major part of his voyage down the Niger.

Sir John Richardson (1787-1867) was a pioneer explorer of the Arctic regions. He is said to be the first to report on the flora and fauna of that territory and was second in command on Sir John Franklin's expeditions.

David Livingstone (1813-1873) who is said to have started the civilization of a continent, graduated from Glasgow and became a medical missionary. Although raised from a humble beginning, he was honored with burial in Westminister Abbey, as a reward for his great contributions. Upon graduation, he sailed at once to South Africa and spent sixteen straight years in missionary work and exploration which included discovery of Victoria Falls. He retired after six more years only for a short visit home but became lost during his next adventure into the jungle. The world was so concerned about this that James Gordon Bennett Jr., of the *New York Herald*, sent Henry Stanley to find him under any circumstances. This mission was fulfilled after two years, making a total of five that Livingstone was out of touch. Their meeting prompted the most famous rhetorical question of all time, namely, "Doctor Livingstone, I presume?" He refused to return and died while still in an effort to achieve his purpose of destroying the slave trade. His body was carried one thousand miles to the Coast by natives and shipped to England. His heart was buried beneath a tree in Central Africa.

Elisha Kent Kane (1820-1857) was born in Philadelphia and graduated from the University of Virginia. He made two trips to the Arctic, the first as Naval Surgeon with the Grinnell Expedition, the second as commander of a private expedition. He planted the American Flag on the most northern part of the land then reached, latitude 80° 35′ N, a record which held for sixteen years. He also charted tremendous coastal areas. After terrific hardships and thirty months spent in the effort, he returned to be greeted with great honors. One portion of Baffin Land is called Kane Basin, and he established one of the earliest polar routes. His descendants settled in Kane, Pa., to preserve the name with several generations of surgeons.

Frederick Cook (1865-1940) a Brooklyn practitioner, accompanied expeditions to the Arctic, Antarctic and South Pacific who claimed to be the first man to ascend Mt. McKinley. The light of his fame was sharply dimmed when this was not substantiated and also when it was proved that Robert Perry discovered the North Pole, rather than Dr. Cook. He also spent five years as a guest of the government for fraudulent oil deals in Texas. In spite of this, he enjoyed a large following of supporters.

Two physicians, Robert McCormick and Joseph Hook, accompanied Captain Ross on the first British expedition, in 1839, to the Antarctic. They discovered the Ross Ice Barrier, called South Victoria Island, and reached a point close to the South Pole. Many subsequent successful adventures into the unknown lands at the poles had several doctors associated as surgeons, botanists, cartographers and zoologists. These men

contributed greatly to the success of these projects.

Sir Wilfred Grenfell (1865-1940) a British medical missionary, a name that is well known to many. He equipped a hospital ship to follow the fishing vessels from the North Sea to Iceland and later established a famous mission with hospitals in Labrador and New Foundland. Besides being the author of numerous books, he lectured in Canada, America and England. Dr. Grenfell formed the International Grenfell Mission and served with the Harvard Unit in France during World War I.

Thomas Dover, whose name has been perpetuated by a popular drug called Dover's Powder, led an expedition of pirates, this band attacked the city of Guayaquil in Ecuador, returning with plunder in amount of 170,000 pounds sterling. He also brought back Alexander Selkirk, a man who had been isolated for four years in the Fernandez Islands off the Chilean coast, after having been put off a ship because of a disagreement with the captain. Subsequently, at a dinner party in Bristol he related the incident and showed his notes to De Foe who created Robinson Crusoe as a result.

There were other pirates and buccaneers from our ranks. Apparently the stigma of that enterprise was not particularly great in those days but rather heroic, lucrative and adventurous.

LITERATURE

There is considerable overlapping in the fields of poetry, literature and drama. Many individuals have such diversified talents that they contributed to all three arts and consequently could well be included in each group but I have avoided this reduplication.

Luke (circa 19-93 A. D.). Without fear of contradiction, I consider St. Luke the greatest contributor to literature of any physician. He was a Greek slave who was converted to Christianity and studied medicine at the Temple of Aesculapius, as Hippocrates did several centuries before him. He was a musician, painter and poet, in addition to being author of the Third Gospel and Acts of the Apostles. The former is said to be one of the most beautiful pieces of literature ever written. It is also said that he attended St. Paul for an attack of malaria somewhere in the Mediterranean at one time.

Moses Maimonides (1135-1204), one of the great towers of strength in Judaism, was an author, rabbi and physician. He was such a great writer that even Mohammedans consulted his works. They covered a wide variety of topics including religion, astronomy, mathematics, philosophy, medicine and others.

François Rabelais (circa 1490-1553) was an extremely learned person who was considered one of the great physicians of his time and ranked with the highest literary figures. Rabelais' career began as a monk but he was dismissed for improper behavior. Following this, at the age of forty-seven, he studied medicine receiving recognition as a teacher and clinician. His writings were often obscene and vulgar but classical and widely circulated. While he was a medical student, he wrote *Gargantua and Pantagruel,* this achieved immortality. Much of the obscenity has been expurgated in the English translation so one can readily imagine what the unabridged editions were like.

Tobias Smollett (1721-1771) graduated in medicine from Aberdeen and served for a time as Surgeon's Mate in the Navy. He is considered to be a pioneer in the development of English novelism and is said to have influenced Charles Dickens and Sir Walter Scott. After experiencing a modest success in practice and a great success in writing, he eventually forsook the former and embraced literature as his career. Smollet is considered a pioneer in stories of the sea. He was the first medical man to create novels and one of three authors who are considered the originators of this type of writing.

Sir Thomas Browne (1605-1682) was a very distinguished scholar and physician whose name has survived for these many years because of his writings. He practiced medicine for a living, writing as a hobby, was a great stylist and has received the highest praise from Sir William Osler, whose

opinion on the subject was considered most critical and sound. Browne's most famous contribution was *Religio Medici* which has been classed with the literary masterpieces and described as one of our most beautiful prose poems. He was elected an Honorary Fellow of the Royal College of Physicians and knighted by King Charles II.

John Arbuthnot (1667-1735), physician to Queen Anne, was a political satirist and orator. The great writers of that time were included among his intimates, and such immortals as Dr. Samuel Johnson, Swift, Pope, Thackery and others, voiced the highest praise for his literary ability. Arbuthnot was one of several physicians included in a select class called the Augustans; this consisted of a distinguished group of the 17th and early 18th Century English literary giants. His "History of John Bull" was perhaps the best-remembered contribution and served to commemorate that caricature.

Francis Brett Young was born in 1884, an English poet, descendent from two generations of doctors and a veteran of the First World War during which he served in the R. A. M. C. He has contributed works of poetry, philosophy and fiction. Young gave up medicine after a short career to enjoy a very successful life as a writer which efforts earned him the coveted Tait Prize.

Sir Arthur Conan Doyle (1859-1930) is a name familiar to all, not for his medical skill but rather for his literary contributions. Sir Arthur experienced a varied career, having spent seven months as ship surgeon on a whaler in the Arctic and later serving in this capacity along the African Coast. He was born in Edinburgh and received degrees both in law and medicine from that University but there are conflicting reports as to the success he attained as a practitioner and ophthalmologist. His success in the Boer War was rewarded with a knighthood; later he served his country in World War I with distinction. Like many others, he abandoned his medical career so his entire efforts could be devoted to writing and made a comment at this time to the effect that, he gave up the detection of errors in refraction for the detection of errors in society. This of course, was after he created the Sherlock Holmes series which event began when twenty-six years of age. Dr. Doyle eventually embraced spiritualism in a vigorous manner and wrote on this subject in addition to his historical and literary contributions. To his many accomplishments, he possessed the ability to play an excellent game of billiards, as well as golf and holds the worlds record for having caught the largest dolphin.

Thomas Linacre (1460-1524) was one of the earliest Greek scholars and graduated with honors from Padua following which he returned to England and was appointed physician to King Henry VIII. During his practice in London he enjoyed a very distinguished clientele; later he became a priest and retired from active life. Even to this time he is recognized as a great scholar and teacher because of his Latin texts and compositions. He translated many of the works of Aristotle and Galen, thus bringing their wisdom to a larger world. Linacre was the founder and first President of the Royal College of Surgeons and his memory has been preserved through the creation of a chair in anatomy at Oxford which bears his name.

John Brown (1810-1882) was born in Edinburgh and practiced there up until the time of his death. He has maintained a high position among physician-authors for over a hundred years. Although he is remembered for his great series of dog stories, other contributions included poetry, drama, art, biographies and other types. *Rab and His Friends* which he created has been called one of the most popular novels ever written. John Brown had a strong style that aroused emotion and endeared his readers.

Thomas Dunn English (1819-1902) lived in the vicinity of Philadelphia, graduated from the University of Pennsylvania in both law and medicine and practiced both professions in Virginia. He was elected to Congress in 1890 but still found time to write poetry, plays and prose. His best known contribution was *Ben Bolt* which was later set to music and included in George

DuMaurier's play, *Trilby,* following which it has enjoyed great popularity. English and Edgar Allen Poe held a great antipathy for each other which culminated in a fist fight. As to the victor, the facts seem to favor the doctor, but I regret to say that Poe won the legal encounter which followed.

Anton Chekhov (1860-1904) graduated in medicine at Moscow in spite of the fact that his father was a serf. There appears to be no record of any success in his profession except as it influenced his writing in many instances. He definitely became a permanent part of the world literature and his plays are said to have revolutionized the modern theatre. His name with that of Tolstoi, is included among the seven giants of 19th Century Russian literature.

John Locke (1632-1704) was an English philosopher, student of the languages and theologian, he lectured and wrote on these subjects at Christs Church, Oxford, before entering medicine. He had close association with Sydenham and Robert Boyle, participating with the latter in the discovery of the law which bears his name. His activities in the cause of civil and religious liberty caused his exile to France and Holland, but he later returned to his native England and continued his work. He wrote prolifically on the subjects of philosophy and the defense of religious liberty with a fundamental constitution for government in his works. Locke is said to be distinguished for presenting to the modern world the largest group of facts on human understanding and is called, "The greatest philosophical medical graduate."

Albrecht von Haller (1708-1777) a Swiss-born physician, von Haller graduated from Leyden and occupied an important chair in the Faculty of Göttingen. The biographers all described his works with enthusiasm, such as, "the greatest systematist after Galen," "the master physiologist of his time," "one of the most inspiring figures in medical history." It appears as if his medical contributions overshadowed the others and his 13,000 scientific papers added greatly to the progress of our science. It must be said, however, that the light of his other successes was by no means dim since he won fame as a botanist, wrote novels, essays and poems. One author describes him as one of the great German poets of the 18th Century.

Peter Mark Roget (1779-1869) a French physician, was the author of a thesaurus which is considered one of the outstanding of all those published.

Theophraste Renaudot (1586-1652) at the age of nineteen received his degree at Montpellier and, after lengthy travel, began to practice but was summoned to Paris by Richelieu to receive the appointment as physician for the King. He failed to please in an extended effort to establish some form of social welfare and left Paris to resume practice. Later under the guidance of the Cardinal, he inaugurated the first French newspaper. Difficulties beset him after the deaths of Richelieu and Louis XIII, and he was forbidden to practice and forced to sever his connections with the paper. He was later appointed historiographer to the King and is described as the "Father of Journalism."

Hendrick Ibsen (1828-1906) studied medicine at the University of Christiana and became such a famous dramatist that he left medical school just short of a degree. He achieved his greatest success with *Ghosts.*

Eugene Sue (1804-1857) was a practicing physician in France, in addition to a career as Army Surgeon. He was considered a famous French novelist and remembered particularly as the author of *The Mysteries of Paris* and the *Wandering Jew.*

T. L. Beddoes (1803-1849) had a varied career and wrote, *The Brides Tragedy* when nineteen years of age. In addition to this, he wrote dramas and engaged in politics. At the age of twenty-two, he gave up literature for the medical profession and received his degree in Zurich ten years later. His appointment as Professor of Physiology was not approved, probably because of his earlier political entanglements.

Charles Lever (1806-1872) although of English ancestry, he was characteristically Irish in his moods and actions. He enjoyed an adventurous life and went to the unsettled

parts of Canada, living with the Indians before settling down to study medicine. After studying at Heidelberg and Vienna, he received his degree from Trinity College in 1831. In 1842 he abandoned medicine for literature serving also in the diplomatic service in Italy. It is said that his novels were as popular as Dickens and Thackery at the time but they most certainly have not maintained that enviable position.

Colonel Fielding H. Garrison (1870-1935) was a great medical historian and wrote one of the most important books on that subject. He had a great literary mind and retentive memory. The work he did in the Army Medical and Surgeon Generals libraries revolutionized the *Index Medicus*. His bibliography was most extensive, being historical to a great extent, however his poems, although few, were most amusing and tended to be risque, these were sent to his intimate friends. He loved music and was a faithful attendant at concerts. It is said that he played the piano well and was a good sight reader. A study of this great man's activities is most instructive and stimulating. Many biographic articles have been written about him and enumerate his accomplishments.

There are two large groups of men in this category that most certainly deserve recognition but space and time forbid details concerning their achievements. These will be treated in an inclusive manner so that it would not appear as if they have been overlooked. Though my comments might be brief, this in no way reflects our lack of admiration for their literary accomplishments.

The first of these represent a group that have gone down in history for their medical contributions but nevertheless, have achieved posterity for cultural contributions also.

Sir William Osler (1849-1919). In addition to his extremely important scientific work, Dr. Osler gave us historical, biographical and literary masterpieces. He accumulated a catalogue containing 1300 items with combined medical and literary interests. He was a great critic of the novel, did much work in bibliography and as you might assume, was an avid reader. He became President of the British Classical Association and it is said that he served as an inspiration for some of Kipling's material.

George David Stewart (1862-1933) was an eminent New York surgeon who graduated from Bellevue in 1889. He held a list of distinguished surgical appointments in New York Hospitals and the presidency of several prominent societies, not the least of which was the American College of Surgeons. His poetic contributions were beautifully composed and have been handed down.

John Chalmers DaCosta (1863-1933) of Philadelphia, is a name familiar to surgeons because of his textbook and important contributions to our specialty. Although he was one of the great surgeons during his era, he contributed poetry of a classical type that has been included in a recently published volume.

William Sidney Thayer (1864-1932). A graduate from Harvard in 1889, Thayer served under Osler at Johns Hopkins, later assuming the rank of Professor of Medicine and Physician-in-Chief at the institution. He was a distinguished physician-teacher, researcher and soldier, and although he enjoyed a large practice, was able to publish two volumes of verse, including translations from the Russian.

Harvey Cushing, a man of great culture, wrote biographies, including one on Osler which was considered a classic and won the Pulitzer Prize in 1926. He also contributed *Memoirs of the First War* and *A Surgeons Journal* in addition to his vast number of scientific treatises.

Havelock Ellis (1859-1940) wrote prolifically on sex education. He was a pioneer in this field at a time when this subject was a matter that was not discussed openly. In addition to his books and essays on this topic, which helped to open the doors and disseminate information, he wrote poetry, texts, papers on heredity and eugenics. He was one of the original proponents of birth control and Womens Suffrage. His sonnets, which were written before studying medicine, and published forty years later.

Richard Cabot is an excellent example of an author who gave advice through his writings.

Thomas Henry Huxley (1825-1895) graduated in medicine and became a great 19th Century English biologist. He achieved a lasting reputation for his theories and writings on evolution, philosophy and theology.

Claude Bernard (1813-1878) was a French physician and physiologist of lasting renown. He was a dramatist, wrote comedies for vaudeville and *Arthur of Brittany,* a five-act play, before studying medicine. At the time of his death his scientific prestige was recognized by the first state funeral that was ever voted for a scientist by the Chamber of Deputies.

Stephen Paget, the son of Sir James Paget, was a great orator and wrote *Confessio Medici.* Lord Moynihan said he was supreme among physicians and the greatest of our orators among surgeons.

Sir Berkeley Moynihan and Sir Humphrey Rolleston were both writers of no mean ability and men of great culture. Interestingly enough, they have each written on this subject.

Richard von Volkman wrote under a nom de plume.

Charles Ricket the discoverer of anaphylaxis, also wrote under a pseudonym.

Edward Jenner (1749-1823) wrote verse, poetry and was also a flutist and violinist of note.

Ambrose Pare wrote sonnets and short verse. Von Hemholtz wrote an epic on acoustics. Trendelenburg wrote important articles on the mechanics of bow and string instruments.

There is a second rather formidable group which is the converse of the latter. These authors are remembered for their contributions not in medicine but from the literary standpoint. In most instances they are contemporary and the fact that they acquired a degree in our profession, was in many instances an unexpected discovery.

Somerset Maugham was born in 1874 in Paris, graduated in England but practiced very little. He wrote his first novel while house physician at St. Thomas and became well known as a playwright and novelist. *Of Human Bondage* is perhaps his best known work. Maugham had the distinction of having four of his plays running simultaneously in London. Although popular but not great, he was called the most readable story-teller of our time.

Archibald Joseph Cronin, born in 1896, graduated from Glasgow and practiced in England and Wales. He retired from medicine in 1931 so that he could devote his entire efforts to writing. Among many popular novels, he created at least one best seller, *The Citadel.* He is now living in Connecticut.

Axel Munthe was born in 1857. Although he was born in Sweden, he became an Englishman who practiced in France and Italy. He also produced among other novels, a best-seller which is well remembered, *The Story of San Michele.* This was a strong type of novel which was written when he was threatened with impending blindness.

Henry de vere Stacpoole born in 1865 was an English practitioner. He published poetry, translations and was the author of many popular novels, including, *The Blue Lagoon.*

Warwick Deeping was born in 1877 and graduated from Cambridge. He was the third generation of physicians in his family. After one year, he abandoned his profession for literature. Deeping produced many novels, the greatest of which was *Sorrell and Son.*

Hans Zinsser (1876-1940) was a great bacteriologist and immunologist. He graduated from Columbia and was associated with Harvard Medical School but traveled over the world in the study of epidemics. Zinsser wrote sonnets, an autobiography and a book which achieved great popularity *Rats, Lice and History.*

Arthur Hertzler (1870-1946) was an Iowan who graduated from Northwestern University, studied in Europe and taught surgery in Kansas. In addition to a textbook, he wrote an autobiography which enjoyed a very wide circulation, *The Horse and Buggy Doctor.*

Victor Heiser's, *An American Doctor's Odyssey,* like the above mentioned novel of Hertzler's was a best-seller.

Frank G. Slaughter was born in 1908 and graduated from Johns Hopkins in Medicine in 1930. He now resides in Jacksonville, Fla., and began writing shortly after he received his degree. He has produced many popular novels, an occasional play and some short stories. His books have received widespread popularity and gained him definite recognition as a writer. In addition to his literary success, he is certified by the American Board of Surgery.

This list could go on in a much longer manner but these examples seem sufficient to demonstrate the fact that in many instances the gift of writing either overcame or overshadowed the medical success of many individuals.

MUSIC

Music, like the other fields we are discussing, encompasses two groups, namely, those with important names in medicine who have made creditable contributions in some other activity and those whose names are unimportant or unknown as members of our profession but who have become famous for outside accomplishments. In my references I encountered one which contained notes on over two hundred of these fascinating individuals in music alone. Bacon has said, "the genius of music and medicine are alike," so perhaps the fact that Apollo was the God of both Medicine and Music has some significance. Music has been used as a therapeutic adjunct to the healing arts in many ways for generations.

The participation of doctors in the realm of music varies from countless soloists to symphony orchestras such as exist in Los Angeles. There are many other units of intermediate sizes composed entirely of physicians. Perhaps some of the men in this Society belong to the Doctors' Orchestra in Akron which is composed of thirty-six members. They rehearse diligently through the fall and winter for the concerts which they give later.

Alexander Borodin (1834-1887) the son of a Russian Prince, is considered the greatest of all musicians who were members of the medical profession. After graduating, he became an army surgeon and Professor of Chemistry in the St. Petersburg Academy of Medicine at the age of twenty-eight and enjoyed a brilliant career in both medicine and music. His closest friend was Liszt. Borodin wrote both symphonies and operas, was credited with the introduction of a specific type of ballet, and was ranked with the most popular of Russian composers. One of his operas was completed by Rimsky-Korsakov after his death, this was titled, *Prince Igor,* and was perhaps his greatest contribution.

Hector Berlioz (1803-1869) a Frenchman, has been described as the greatest musician associated with medicine but must relinquish this honor to Borodin since he forsook our profession before completion to pursue the arts. His name has been perpetuated because of his genius and great compositions; this is attested to by the fact that he won the Grand Prix de Rome and Legion of Honor. His father was a doctor whose disappointment at the withdrawal from medical school was manifested by cutting off his son's financial support.

Theodore Billroth, born in 1829, was a great pioneer in visceral surgery and an outstanding pianist who in addition to his medical degree, had a complete education in music. It is said that he was one of the outstanding 19th Century leaders in surgery and music. In addition to his exceptional ability to play the piano, he wrote a book on the psychology of music, composed songs and later became a capable viola player. Both of Billroth's grandmothers were opera singers but in spite of this heritage and the fact that he became an excellent pianist while still a youth, he abandoned the idea of a musical career as early as nineteen years of age. He served as an accompanist to Jenny Lind on her visit to Göttingen while still studying surgery and conducted an orchestra in Zurich while Professor of Surgery. Brahms was his closest associate, and most of the chamber music he

composed was played with Billroth's accompaniment and at his house for its first trial. Many of the biographies on Brahms contain reference to him and that immortal composer dedicated his C and A minor quartets to Billroth, in addition to presenting him with the manuscripts.

Leopold Auenbrugger, who was the Father of Ausculation, wrote great librettos for the opera. He composed the music for the Salieris opera, *The Chimney Sweep* and became a great favorite of Maria Theresa.

Florient Kist, a Dutch physician, is included among the most famous musicians from that country. He practiced his profession at the Hague and in addition to his great ability to play the flute and coronet, composed some of the greatest pieces for these instruments. Kist also organized musical societies and founded a journal dealing with music.

William Kitchener born in 1775, an English physician, educated at Eton and Glasgow was considered eminent as a doctor-composer of the 18th Century. He also distinguished himself in literature as the author of several rather unusual works.

Hermann Ludwig Ferdinand Von Helmholtz (1821-1894), one of the great physiologists in our memory, occupied the chair in that science at various Universities in Germany and made important contributions. His original work on optics and the invention of the ophthalmoscope seem sufficient to preserve his memory, but he also left a mark in the history of music. He was a great musical theorist who invented a system of double harmonics and developed the physical nature of musical sounds which greatly facilitated teaching and appreciation. He also contributed the theory of classical *Tonefindugen* (tonal sensations) and inspired the later development of this.

William Savage Pitts (1830-1918) was a graduate of Rush Medical College, class of 1868, who achieved a wide following and splendid reputation as a general practitioner in Iowa. Although he composed many songs and poems, his fame rests on a single contribution, *The Church in the Wildwood*. Approximately 100,000 visitors a year make a pilgrimage to this church which has been restored by the Society formed for its preservation.

Leopold Damrosh, father of the well-known contemporary conductor and composer was a physician who abandoned his profession to become a concert violinist. Wagner and Liszt were numbered among his close friends. Many of the German operas received their American debut under his baton.

Kasper Bartholin (1585-1629), a name we readily recognize, made an important study of the Grecian double flutes.

Hermann Boerhave (1668-1738) was a great Dutch chemist, physician, teacher, botanist and practitioner. He occupied many important positions at the University of Leyden. Monarchs and Princes came to his side for advice and teaching. He is known as the first physician to cultivate chamber music.

John C. Hemmeter was born in 1863. In addition to being a physician, he was a composer and theorist who achieved a high place in the musical world. He composed a cantata for male chorus and full orchestra entitled *Hygea*, which was dedicated to Dr. William Welch.

Fritz Kreisler was born in 1875. His name is familiar to all of us as one of the great violinists. After a successful concert tour of the United States early in his life, he gave up music and studied medicine, later becoming an officer in the Austrian army. He was also a composer, the most famous of his contributions being the *Caprice Vienoise*. The Grand Prix de Rome was awarded to him at the age of twenty and the Grand Prix for the Paris Conservatory when he was twelve. Kreisler wrote a book and an operetta; the latter was produced in New York City.

Richard Shuckbugh, a British Army Surgeon, is recognized as the composer of *Yankee Doodle* in 1758. He was attached to General Abercrombie's army at Ticonderoga, just south of Albany. It became gloried by the American soldiers after the Battle of Bunker Hill.

James B. Naylor, a graduate of Starling Medical College in Columbus, Ohio, represents a lighter vein in musical contributions by physicians. He is the composer of *Casey Jones* and *A Hot Time In the Old Town Tonight.*

George Ethridge was one of the very early noted English composers. He lived during the 16th Century and is considered one of the famous musicians of his day. He was recognized as possessing great ability as a physician in addition to these aforementioned accomplishments. He occupied the chair in music at Oxford University which is considered a rare honor.

Albert Schweitzer was born in 1875, in Alsace. He was recognized as a philosopher, theologian and musician. His life was dedicated to missionary work in French Equatorial Africa and he studied medicine at the age of 30 in Strassburg. Dr. Schweitzer was an accomplished organist and is considered a world authority on the music of Bach, in addition to several other classical and theological subjects. His medical expenses were financed by the volumes which he wrote on Bach, the biography being considered one of the greatest works written on the master Scientifically, Schweitzer also achieved worldwide recognition for his work on tropical diseases and even though eighty years of age, has published an article on this subject in a current issue of *The Journal of the American Medical Association.* He was the recipient of the Nobel Peace Prize in 1952. The descriptive phrases that are used to eulogize this man are well merited and defy comparison. To mention a few, they follow these lines, "number one man in the world", "the man of the Century", "the most remarkable man of the age", "the greatest genius since Leonardo DaVinci". I could continue, but this should serve to illustrate his greatness and character.

POETRY

This list is formidable and contains many famous names, some wrote poetry on medical subjects but we are particularly concerned with those who acquired greatness through their contributions. It has been stated that we are all poets at heart and that medical poets are not of as high a quality as general poets, i. e., "not as poetic a poet". This is apparently disproved by many famous exceptions, as you will see.

Much has been written on the struggle between medicine and poetry, whether to support the one and deny the other. Many have written under a pseudonym; others wait until they are on the way to retirement before indulging openly in their taste for writing poetry. Several ancient medical men existing as early as 150 B. C. contributed to the poetry of their era. The earliest known medical poet was Empedodes, in 500 B. C.

John Keats (1795-1821) in a short life span of 25 years, became a physician and one of the famous English poets. Although he never formally attended a University, the abandonment of his profession for a literary career seems justified since he has been called the greatest of Shakespeare's successors. Osler has written a paper about him. The first line of his Endymion, "A thing of beauty is a joy forever" has been immortalized, this was composed during the first years of his study.

Oliver Goldsmith (1728-1774), Irish-born son of a clergyman, he was designated the greatest physician contributor in the 18th Century of anything worthy of mention. He wandered over Europe playing the flute and debating for a living. Goldsmith failed his examination at the College of Surgeons and was turned down as a surgeon for the Royal Navy. He worked at many things including medicine but gave this up because of a disagreement with an apothecary as to the dose of a drug, but was later given an honorary degree of Bachelor of Medicine. Dr. Johnson spoke as follows concerning Goldsmith, "there was no kind of writing he did not touch, none that he touched that he did not adorn". This about a man who was an utter failure at everything he attempted until he reached the age of 31. Among his many contributions, *The Deserted Village* is considered greatest and his best known play, *She Stoops To Conquer.*

Robert Bridges (1884-1930) retired from practice when 37 years of age to follow a literary pursuit. He felt that his contact with humanities made him a better poet but decided the latter career was more important. This was in spite of the fact that he was considered a successful pediatrician. His first work was a volume of lyrics published in 1873, while a medical student. Bridges was Poet Laureate in 1913 and received the Order of Merit in 1929. He acquired a profound learning and his position among English poets was very high, this fame has continued to increase since his death. According to the records, he was the only Poet Laureate of England who was a medical man even though there is a large group of prominent English poets who were also physicians. I can only mention some of these in passing in spite of the fact that their achievements merit much greater detail.

Samuel Coleridge (1772-1834) was the author of *Rimes of the Ancient Mariner* which has long remained a classic.

Thomas Lodge (1558-1625) studied medicine at the age of forty, after considerable success in literature. He was a great lyrical poet, author of plays, a successful physician and member of the Royal College of Surgeons, in addition to being a lawyer and soldier. His lyrics were considered among the finest in the English language. His most interesting play was *Rosalynde* which provided Shakespeare with the inspiration for *As You Like It*. Lodge also supplied the idea for his *Venus and Adonis* with *Glaucus and Scilla*. He published a book of sonnets, lyrics and poems, also composed songs and madrigals.

Thomas Campion (1567-1620) was a physician, lawyer, poet, musician and contemporary of Shakespeare. He was considered one of the lyric masters of English poetry also one of the very great poet-physicians and among the leading Elizabethian poets of the 17th Century. Lodge was likewise classed in this category.

Samuel Garth (1661-1719), physician to George I, wrote satirical poetry to which his contemporary physicians took exception. He overcame their disfavor when elevated to knighthood and was appointed physician in General of the Army.

Mark Akenside (1721-1770) likewise was an accomplished physician and poet. He was the son of a butcher, physician to the Queen and a member of the Royal College.

George Crabbe (1754-1832) a physician and poet from England. During this highly competitive era, Crabbe achieved great success in the latter.

Edward Jenner (1749-1832). The discovery and use of vaccine is testimony to Jenner's fame as a physician. He wrote classical poetry as well as verse which were of sufficiently high quality to classify him as a poet, in addition to being one of our great and immortal medical scientists.

Bernard Mandeville was born in Holland but came to England when 21 years of age and was unsuccessful in his medical practice. He wrote poems which although unconventional and controversial, achieved great popularity and left his name for posterity. His *Fable of the Bees* is still called one of the most powerful philosophic and cynical poems in English.

Sir Richard Blackmore (1650-1729) a graduate in medicine from Padua, Dr. Blackmore received great praise for his poems which he wrote while going on rounds. One of these was a great philosophical poem, *The Creation*, which Dr. Johnson and other important critics accorded high acclaim. Dr Blackmore was the founder of the famous Kit Kat Club. He also wrote a pamphlet entitled, *A Stayr Against Wit* which made him the "best-hated figure of that time."

There are many others in this class of great physician-poets from England and at the risk of some omissions, I will leave them with the comment that they appear to have achieved the greatest fame and represent the most outstanding group of any era or from any nation.

Germany was a country of great culture and has left us names of physicians long to be remembered for poetic contributions. The greatest of these were contemporaries and

each has left his lasting mark on the culture of the world.

Johann Goethe (1749-1832) has been referred to as the greatest figure in German literature and is said to have studied medicine to broaden his knowledge. His most important work was *Faust* from which Gounod composed the famous opera. He was also recognized as a novelist, dramatist and etcher.

Johann Cristoph Friedrich von Schiller (1759-1805) was greatly influenced by Goethe. He first wrote prose and poetry while a medical student. Biographers have classed him as second only to Goethe, whom he is said to have saved from despair and discouragement in his literary efforts. One reference mentioned him as the greatest of medical poets. This of course, is a matter of opinion, as John Keats has been described in the identical words. Like many others, he did not confine his writings to poetry but also drama and philosophy. He left a career as assistant regimental surgeon at a salary of $7.50 per month for a literary field. He was the author of *Wilhelm Tell*.

Oliver Wendell Holmes (1809-1894) would appear to be the outstanding figure among the American physician poets and is classified as a poet in the encyclopedia. His fascinating lectures and demonstrations during the 35-year tenure as Professor of Anatomy at Harvard University have remained as classical examples of the teaching art. He is recognized as being the first to describe the infectious nature of childbed fever. His observations having been subsequently elaborated on by Semmelweis, this was before the observations of Pasteur and Lister. Justice Holmes was the son of this great man and went down in history as one of our most famous jurists achieving lasting reputation as Associate Justice of the Supreme Court of the United States for 30 years. Dr. Holmes coined the words, anesthetic and anesthesia. One of the lasting contributions he made to the lighter side at Harvard were his poetical contributions for class reunions. His many works consisted of novels; poems, articles in newspapers and magazines, causing some to refer to him as the "American Goldsmith". It is difficult to decide whether Holmes achieved his greatest fame in medicine or in literature, but it is certain that he attained great heights in both. His verse filled three volumes and he was the author of three novels, in addition to other extensive contributions. Perhaps his *Breakfast Table Series* is best remembered. It is said that he possessed an intense dislike for surgery. Dr. Holmes fulfills my criteria for a genius, since he was able to serve two masters so diligently, as he wrote prolifically in a varied manner while still very active and prominent in his profession. His efforts consisted of scientific articles, poetry, humor, novels and essays. He has been included amongst the four great American poets. This is the man of whom Sir William Osler said, "the most successful combination the world has ever seen of a physician and man of letters".

Silas Weir Mitchell (1829-1914) was a Philadelphian who achieved international fame as a neurologist and is included in all uppermost groups of American physician writers. He wrote his first novel at the age of 53 when he was at the peak of his medical success. It is rather certain that Holmes influenced him as they were contemporaries and friends. His reputation as an author of poetry and fiction equaled that as a neurologist and he is considered by many to be the second greatest American writer physician. Mitchell was the founder of neurology as a specialty. His literary contributions which began with a poem at the age of 17 and a novel after he was 80, filled 18 volumes. They were of splendid quality and covered a varied range of themes. His father, Dr. John K. Mitchell, was also a recognized author. It is said that Mitchell was in part responsible for the coming of Sir William Osler to the University of Pennsylvania and also that he was a patron of Nogouchi's.

Merrill Moore was born in 1903. A neurologist from Tennessee, graduated from Vanderbilt University in 1928, he practiced in Boston and was associated with Harvard Medical School. During the last war he was decorated with the bronze star for service in

the South Pacific theatre. He has a distinctive style and his enthusiasm seemed unlimited since he turned out about 50,000 sonnets before reaching the age of 40. His father was a novelist.

Canada has given us at least two very prominent physician-poets. William Henry Drummond (1854-1907) was born in Ireland but emigrated to Canada at 10 years of age, graduated from medicine at Bishops College which later was taken over by McGill University. He was inclined to ignore the grammatical phase and write phonetically. Consequently, his verses in the patois of the French Canadians, became classics. He combined his practice with literature, demonstrated great originality and has been called, although somewhat unofficially, the Poet Laureate of British America. I can remember distinctly one night in Quebec, the pleasure appreciated by my guide when I read him one of Drummond's poems. This was even in spite of my terrible dialect.

John McCrae (1872-1918) was born in Guelph, Ontario, graduated in medicine from the University of Toronto in 1898. He was a distinguished artillery officer in the Boer War, after receiving his medical degree. Following his internship in Toronto at the General Hospital, he became resident at Johns Hopkins, then served in Pathology at both McGill University and Montreal General Hospital. Dr. McCrae collaborated with Sir William Osler in writing a textbook bearing their names. He was a prominent contemporary poet and his greatest work, *In Flanders Field*, which was published anonymously in *Punch*, is considered by some, to be the most lasting poem of the First World War. During this conflict he served an active career in the field as Commander of General Hospital No. 1 and died of pneumonia. He demonstrated a superb quality and great simplicity in his verse.

Two additional American poets that have come to my attention are: Joseph Rodman Drake (1795-1820) who practiced medicine in New York City and achieved fame as a poet and satirist. He wrote verses for the *New York Evening Post*. Among the many poems which he wrote *The American Flag* was perhaps greatest. This was recited at patriotic gatherings for years. A book has been written on the works and accomplishments of Dr. Drake.

Thomas Holley Chivers (1809-1858) a contemporary rival of Edgar Allen Poe, Dr. Chivers studied medicine in Lexington, Ky., at Transylvania University and obtained his degree with distinction in 1830. He published many books and poems. Poe, in his biography, referred to him as, "one of the best and one of the worst poets in America". This observation was even more interesting when one considers that their styles of writing were very similar.

Although this list of physician-poets may seem lengthy to you, it is amazing to note that the cumulative index for this group recognizes 411 individuals.

PUBLIC LIFE AND POLITICS

Many of our confrères have strayed into the field of politics and public life, either as an avocation or a career. This was brought forceably to my attention when the Puerto Rican terrorists let loose with guns in the House of Representatives. There were several physician members present to administer first aid. I will mention a few of the more prominent names that have carved their niche with the passing of time. Many were legislators, congressmen, senators, governors and cabinet members.

Ugo Benzi (circa 1376-1439) known as Hugh of Sienna, Dr. Benzi received his Doctors degree from the University of that name and was Professor of Medicine at the same institution, followed by a similar position later at Bologna and Parma. His published work is claimed to be the earliest written in a common tongue. He occupied important positions in other parts of Italy, including the Vatican and was a lecturer at the Sorbonne. Benzi was a great philosopher and is described as the medieval world's most famous physician.

Jean Paul Marat (1743-1793) was born in Switzerland. There is a conflict as to where

he studied medicine, one reference mentions Bordeaux and another London. In either event, he practiced in each place and wrote articles in both languages acquiring a reputation for his work and writings. One of the latter was violently assailed by Voltaire for its materialism. Charles X of France recognized his ability giving him a generous allowance as surgeon to his guards. It was for a political life that he replaced his scientific career in 1789 and gained notoriety. Dr. Marat was a violent revolutionist and founded a journal in which he expressed his vehemence. The opposition forced him underground during which he published his paper from various secluded places including the sewers of Paris. Eventually, he was stabbed to death by Charlotte Corday, a member of the opposition. His assassination was exploited with ceremonies and even by a painting done to commemorate it, in addition to a cult which continued his teachings.

Sir Starr Jameson (1852-1917) received his medical degree at London in 1877 and was a member of Parliament from Kimberly. He will always have his name associated with the Transvaal Raid. Starr Jameson was knighted and was eventually influential in the colonization of South Africa as an associate of Cecil Rhodes.

General Leonard Wood (1860-1927) a graduate of medicine from Harvard in 1884, practiced in Boston. He has been called the greatest colonial administrator America has ever produced. Harvard later conferred an honorary degree on him. Wood won the Congressional Medal of Honor for service in Arizona against the Apaches, eradicated yellow fever from Cuba while serving as Governor General and served as Chief of the General Staff of the United States Army. He transferred from medical to line officer voluntarily. Later, he served as Civil Governor in the Philippines for three years. At the time of his departure he left them with a peace and prosperity which had not existed previously.

Georges Clemenceau (1841-1929) graduated in medicine from the University of Paris and was the third generation of Doctors in his family. He was a born leader, well educated and assumed a radical attitude towards government and social conditions early in life. He came to America shortly after the Civil War because his native country was not particularly safe for him at the time. It is said that he taught French in a private school, practiced in Connecticut during this time and married a girl from Massachusetts, who was one of his pupils. After three years, he returned to Paris and resumed practice. This eventually was replaced by journalism, oratory and politics. His title, "The Tiger," was well deserved and earned. The succession of positions he held led through many ranks serving as, Mayor of Montmarte, Member of the Chamber of Deputies, Member of the Senate, Premier, and Prime Minister of War. Eventually he was called "The Saviour of France" and played a very important role in forming the Treaty of Versailles, as the climax to a very active career.

Joseph Lister (1827-1912) a famous name in medical history, he was the founder of antiseptic surgery. He married Symes' daughter, was very active in research on varied surgical problems and was successively Professor of Surgery at Glasgow, Edinburgh (succeeding Symes) and Kings College in London. Lister was the President of the Royal and British Societies, created a Baronet, then raised to a peerage four years later. Dr. Lister was the first medical member of the House of Lords.

Virchow was a writer on economics and also a member of the German Legislative bodies including the Reichstag.

Lyman Hall (1724-1790) was a great patriot at the time of the American Revolution. He was born in Connecticut and graduated from Yale in 1770. I know nothing concerning his medical achievements but he led an active life being at various times a minister, member of the Continental Congress, Governor of Georgia and signer of the Declaration of Independence.

William Henry Harrison (1773-1841), the ninth President of the United States, studied medicine at the College of Physicians and Surgeons in Philadelphia. His father,

a prominent Virginia politician, signed the Declaration of Independence. William Harrison was appointed Governor of the Indian Territory by President Adams, was the first delegate to Congress from the Northwest Territory, grandfather of Benjamin Harrison, the 23rd President of the United States, and the first President to die in office. He was defeated for the presidency by Van Buren in 1836, but turned the tables four years later after winning the Whig nomination from Henry Clay. Daniel Webster was his Secretary of State.

Benjamin Rush (1745-1813) received his medical training abroad, was a great friend of Benjamin Franklin and achieved a literary reputation from his writings on social and medical subjects. He was a surgeon general in the American Revolution, was Treasurer of the mint in Philadelphia and a signer of the Declaration of Independence. Other physician-signers were Oliver Wolcott, the governor of Connecticut, Joshia Bartlett, the governor of Massachusetts and Mathew Thornton, Judge of the Supreme Court of New Hampshire.

Viscount Finlay, M.D. (Robert Bannantyne) a physician, great linguist and classical scholar was appointed Lord Chancellor of England in the formation of Mr. Lloyd George's first government. Later at the age of 80, he was British member of the permanent Court of Arbitration at the Hague.

Sun Yat Sen was the first graduate in medicine from the University of Hong Kong, the first President of the Chinese Republic and attained great fame in China.

You Chan Yang, the Korean ambassador to the United States, received both his medical degree and clinical training in this country following which he practiced in Honolulu for thirty years. During that period he was leader of patriotic and religious groups in Hawaii.

Edward Tiffin, although English born in 1776, he was said to have received his medical education at the University of Pennsylvania. He moved into the Northwest Territory as a pioneer with only one other family. Strangely enough four of the outstanding individuals in the history of this section were either physicians or had studied medicine. The other three were, Arthur St. Clair, Nanasseh Cutter, and William Henry Harrison. Tiffin became the first Governor of Ohio and Harrison the President of the United States.

Ray Lyman Wilber, a Doctor of Medicine, was Secretary of the Interior from 1929 to 1933 and President of Stanford University from 1916 to 1943. His death in 1949 brought the end to a very illustrious career.

Henri Queielle, a physician, was Premier of France from September 1948 to October 1949. He was not particularly prominent in this field and more or less served as an interim officer.

Raymond Graw San Martin who became President of Cuba in 1944, was also a Doctor of Medicine.

John XXI, a native of Lisbon, was Pope from September the 8th, 1276 to May the 20th, 1277. Actually he was John XX but an error in reckoning gave him the title he was known by. Some biographers referred to him as a magician but I am at a loss to explain this description. In addition to being a physician, he was also the author of several medical and theological books. He was killed when the roof of a palace he built caved in.

Nathaniel B. Shurtleff was a physician in New England colonies in the middle 19th Century. He was a prominent collector of rare books and printed an important historical record of the Bay and Plymouth colonies in 11 volumes. His greatest achievement was accomplished by a rare bit of intrigue when he tricked Deacon Lathrop of Old South Church to exchange one of the rare Bay Psalm books for some relatively insignificant volumes. This is described in an interesting article published in a recent Life magazine that states at present prices he received a value of $250,000 in exchange for only $15. The prize now resides in the Brown Library at Providence. Doctor Shurtleff served three terms as Mayor of Boston.

In the 1954 Congressional elections, four of five incumbent physician members of the House won election. Another lost in a bid for a Congressional seat.

SPORTS

I am quite certain that this is probably the most common extracurricular activity that doctors are attracted to. Many have excelled at intercollegiate sports; then gone on to coaching positions and professionalism. We were able to obtain names of only a few really famous and outstanding examples but there certainly must be more.

Dr. Robert Brown received his medical degree and served his internship while an active member of the New York Yankees baseball team. His ability as a third baseman was outstanding and he holds several records, both in the regular season and the World Series, even though he missed part of the games for his studies. After two years in Korea, he played in 1954 until the end of June when he left the sport permanently to begin his residency in California. When asked what he was going to specialize in the reply was, "the vivisection of umpires."

Hubert Pruette, an obstetrician in St. Louis, Missouri, was an American league pitcher. He was a regular and has the unique credit of fanning out Babe Ruth 17 out of the 23 times he pitched to him.

As a physician whose sport was non-athletic, the London practitioner, Henry Jones may be mentioned as "the supreme authority on whist." He wrote under the pseudonym of "Cavendish."

William Gilbert Grace (1848-1915) was born in England and represented a family of cricketers that included an uncle, father, brothers, and his son. He was an excellent athlete, endowed with a superb physique, was called "The Champion" and engaged in top cricket matches for 36 years. He retired with many great records and although a physician, managed the London Cricket Club upon leaving competition. As captain of several famous teams, he toured extensively receiving many prizes and honors. Many consider him the greatest cricket player of all times.

Roger Bannister achieved the coveted honor of being the first human to break the four-minute mile. After waiting for centuries until this was accomplished, his time of 3:59.4 was bettered only one month later by an Autralian, at 3:58. Bannister was notified on July 9th, 1954, that he had qualified as a medical doctor at St. Marys Hospital in London and raced that evening. In my opinion his was a great achievement because as long as I can remember it has been said that the day would come when some one would be able to run that fast. His name is now being considered by Queen Elizabeth for a Knighthood. The most recent report was that he gave up running because of the inability to keep in training while pursuing his duties as a resident, which fact I can easily understand.

SCIENCE AND INVENTORS

Many men, trained in medicine, have made important contributions in physics, mathematics, chemistry and astronomy or have produced notable inventions.

Omar Khayyam (circa 1020-1123 A. D.) was considered the greatest Persian mathematician. He was also a philosopher, astronomer, poet and evidence proves that like many other scholars of that era, the study of medicine was included with his other pursuits. He treated the son of a Sultan Sanjars for smallpox and although the outcome was successful, he fell into some disrepute because of a pessimistic attitude he assumed during his illness. It is documented that he studied medicine and was a successful practitioner. In spite of the great fame which the *Rubaiyat* brought him, he is considered by some authorities to be little known as a poet in Persia and one whose work was not highly regarded. He also accomplished a complete reform of the calendar.

Avicenna (979-1037) an Arabian physician, was considered to be the greatest philosopher and theologian of that era. He wrote books numbering a hundred or more on many subjects, in addition to medicine

and philosophy, these included mathematics and astronomy. His study on the formation of mountains gained him the title, "Father of Geology." The contributions he made to the progress of medicine prompted at least one author to praise him as the greatest physician from Galen to Vesalius, a period of 1300 years. He popularized the use of ligatures for the control of bleeding even before Paré.

Nicolaus Copernicus (1473-1543) was a native of Poland and received his degree from Crakow following which he did work at the University of Padua and the University of Bologna. He was a great mathematician and astronomer who revolutionized that science upsetting the religious teaching of that period by his theories. It was his contention that the planets moved around the sun and the latter was the center of the universe rather than the earth. His death which occurred a few hours after publication of the book, undoubtedly saved him from reprisals of a severe nature.

Galilei Galileo (1564-1642) was born to a noble Florentine family and studied medicine at Pisa. Like many of his time, he was endowed with great natural gifts of ability, learning and observation. These included mathematics, music, art, astronomy and others. While Professor of mathematics at Pisa, he radically opposed the teachings of Aristotle and maintained that weight did not influence the speed of falling objects. When he proved this by dropping two iron balls of different sizes from the leaning tower before a large group of Professors, their antagonism was so great that he was forced to resign from the chair. Later in reward for his research and invention of the telescope, he was awarded a lifetime professorship by the Venetian Senate with a high salary. His many original contributions and observations class him as a great genius. Among these were the isochronism of the pendulum which he checked with his own pulse while in church watching a lamp swing, another was that the path of projectile was a parabola. His perfection of the telescope led to astronomical observations which confirmed the Copernician theory. These were at a variance with the teachings of the Church, consequently, he was summoned and as a result signed a statement asserting that he did not believe his findings. When a second publication appeared some years later, his retraction failed to keep him from prison. He was released upon the insistence of friends to be placed in banishment and under guard.

Paracelsus (1493-1541) was an extremely radical medical thinker during his period, who attacked the foundation of ancient medicine and discarded dogmatism. He dealt with alchemy and astrological observations with a tendency towards mysticism. In spite of these characteristics, he managed to inscribe his name for posterity and a monument in Salzburg commemorates him. He was considered a great physician by many, his father was a doctor and his mother a Hospital Superintendent. Paracelsus studied minerals, the mechanics of mining and the diseases of miners. There can be no question that he attained a high place in history because he did much to change the thinking of that period.

Joseph Ignace Guillotin (1738-1814) was a very successful Parisian practitioner and was reputed to be outstanding. He was one of the first proponents of vaccination but his name has been handed down through history not for his medical fame but rather because of a decapitation machine that he devised. Guillotin is classed as a great humanitarian and an ardent supporter of the French Revolution. His interest in social welfare led him to advocate this method of doing away with political enemies because it was painless and quick. Hitherto such consideration had been reserved for nobles and the common classes suffered cruelty and torture in their annihilation.

Richard Jordan Gatling (1818-1903) a graduate of Ohio Medical College in Cincinnati is credited with the invention of many original farm machines including which was perhaps the first motor driven plow. His fame arose not from this accomplishment but because he invented and patented the first rapid fire weapon. This bore his name,

was the forerunner of the modern machine gun and became officially adopted by the United States Army.

Luigi Galvani (1737-1798) a physiologist and anatomist occupied the chair in these two sciences at the University of Bologna. During his laboratory work he observed that an electrical impulse caused muscular contraction. This aroused his scientific curiosity to the extent of becoming a pioneer in electricity and the discovery that chemical action can produce a current which led to the invention of batteries, and many other electrical processes which bear his name.

Robert Boyle (1627-1691) was born in Ireland and studied medicine at Oxford under Sydenham where he obtained his degree in 1655. In addition to being a physician, he was a chemist, theologian, philosopher and great scholar. After studying under Galileo he conducted important research in the chemistry and physiology of respiration. The law in physics which bears his name deals with the volume of gases under conditions of temperature and pressure.

Karl Von Welsbach (1858-1929) was an Austrian physician who accomplished many discoveries in chemistry. His name was perpetuated through the invention of a gas burner and mantle for gas light. This can perhaps be recalled only by the older members. He also devised a type of incandescent electric lamp.

John Gorrie (1803-1855) was a graduate from P & S in New York but practiced for a while in his native South Carolina before moving to Florida. Although a successful practitioner, he occupied many public offices and later became Mayor. During the process of controlling the air in sick rooms, he developed the principle for artificial refrigeration and was granted the first United States patent for this mechanical method. Statues were erected to his memory, one in Florida by the Southern Ice Exchange, the other in Statuary Hall at the United States Capital in Washington.

William Prout (1785-1850) was an English physician and chemist who did extensive research, advancing the hypothesis that bears his name. This considers hydrogen as a primary substance and that the atomic weights of the other elements are exact multiples of it. The concept involved was part of the basis for the modern atomic theory.

Henry Draper (1837-1882) a graduate in medicine from the University of the City of New York, Dr. Draper became Professor of physiology but eventually devoted his interests to astronomy. After constructing his own telescope, he was able to make the largest picture of the moon up to that time. Congress awarded him a gold medal for his achievements which included the discovery of oxygen on the sun. This was the first recognition of a scientist by Congress.

CONCLUSION

As a closing observation, to emphasize the frequency with which "The Physician's Alter Ego" manifests itself, it is interesting to note that, following the establishment of a chair in music at Oxford during the 16th century, the first five men to fill this professorship were all physicians.

After this somewhat sketchy summary on a subject about which books could be written, I will leave you in the hope of stimulating a wider interest in this matter. It seems unlimited and encompasses all branches of culture, adventure, science, sports, and many other activities, reaching from the Greek Gods and Apostles, to modern athletes.

Our profession has left a mark on the history of civilization that can be approached by few, if any, other groups of individuals. We should be justly proud of our heritage.

40 West North St. (2).

BIBLIOGRAPHY

1. A Dictionary of Music and Musicians., George Grove, London, Macmillan and Co., 1879.

2. Abraham Gesner, M.D., Surgeon Geologist., Canadian Medical Association Journal, 59: 384-387, October 1948.

3. Aesculapius Among The Augustans, Annals Medical History, 6: 521-528, November, 1934.

4. Afterthought or Memorandum on Medical Poets., Bulletin Medical Library Association, 29: 199-201; June 1941.

5. A History of Medicine, Arturo Costiglioni., Alfred A. Knopf, New York 1941.

6. Alexander Anderson, M.D., First Wood Engraver in America., New York State Journal Medicine, 43: 440-446, March 1943.

7. A Medical Geologist, William Henry Fitton., British Medical Journal, 1: 195, February 1942.

8. American Doctors as Men of Letters., Bulletin Historical Medicine, 13: 507-513, May 1943.

9. American Doctors in Other Fields., Historic Medicine, 35: 41, 87-95, February 1939.

10. American Doctors in Other Fields., Southern Medicine and Surgery, 100: 439-493, 561-620, November 1938.

11. American Doctors in Other Fields., Southern Medicine and Surgery, 100: 621-627, December 1938.

12. American Doctors in Other Fields., Southern Medicine and Surgery, 100: 494-498, October 1938.

13. American Doctors in Other Fields., Southern Medicine and Surgery, 100: 440-445, September 1938.

14. American Doctors in Other Fields., Southern Medicine and Surgery, 35: 41-101, January 1939.

15. American Physicians as Poets and Fiction Writers., Bulletin Medical Library Association, 32: 73-84, January 1944.

16. An Address: Literature and the Clinical Point of View., Medical Journal of Australia, 2: 26, 481-486, December 1945.

17. Annals Medical History, Vol. 8, 1926.

18. Annals Medical History, New Series, Vol. 7, 402, 1935.

19. Art as Top-Ranking Medical Hobby., Bulletin New York Academy of Medicine, 27: 378-381, June 1951.

20. Axel Munthe, Swedish Author and Physician., Biography New Times, 17, February 1949.

21. Berenclow, B. M., Apollo and Terpsichore (Music and the Healing Art), F. N. Marquet & F. K. Harford. Bulletin Historical Medicine, 21: 639-673, September-October, 1947.

22. Bulletin Erie County Medical Society, N. Y. State 12, December 1945.

23. Bulletin of the History of Medicine, Vol. 13, 1943.

24. Chambers Encyclopedia., Lippincott Company, Philadelphia, 1897.

25. Children of Apollo (Physician-Poets), Annals Medical History, 2: 227-235, March 1930.

26. Claude Bernard., Olmsted & Olmsted, Henry Schuman, New York 1952.

27. Claude Bernard as Dramatist, Annals Medical History, 7: 253-260, May 1935.

28. Connecticut Doctors in Other Fields, Connecticut Medical Journal, 5: 337-343, May 1941.

29. Current Biography., H. W. Wilson Company, New York 1942.

30. Dictionary of American Biography., Vol. 4, Charles Scribners Sons, New York 1930.

31. Doctor Edward Tiffin, First Governor of Ohio, Bulletin Historical Medicine, 21: 811-822, September-October 1947.

32. Doctor Richard Shuckburgh and Yankee Doodle., Annals Internal Medicine, 7: 1548-1552, June 1934.

33. Doctors and Music., Canadian Medical Association Journal, 33: 676-679, December 1935.

34. Doctors and Music., Journal American Medical Association, 156: 6, 24-25, October 1954.

35. Doctors as Artists, Canadian Journal Medicine and Surgery, 74: 1-6, 6-12, July 1933.

36. Doctors as Artists., University Western Ontario Medical Journal, 17: 4, 135-143, November 1947.

37. Doctors as Musicians, Ohio State Medical Journal, 36: 180-181, February 1940.

38. Doctors as Novelists, Postgraduate Medicine, 6: 501-504, December 1949.

39. Doctors as Scholars., Journal Laboratory and Clinical Medicine, 22: 290-293, December 1936.

40. Doctors in Other Fields., Southern Medicine and Surgery, 101: 293-296, June 1939.

41. Doctors in Other Fields., Southern Medicine and Surgery, 101: 242-245, May 1939.

42. Doctors in Other Fields., Southern Medicine and Surgery, 101: 568-570, November 1939.

43. Doctors in Other Fields., Southern Medicine and Surgery, 101: 512-515, October 1939.

44. Doctors in Other Fields., Southern Medicine and Surgery, 101: 338-342, July 1939.

45. Doctors in Other Fields., Southern Medicine and Surgery, 102: 76-79, February 1940.

46. Doctors in Other Fields., Southern Medicine and Surgery, 101: 399-402, August 1939.

47. Doctors in Other Fields., Southern Medicine and Surgery, 101: 455-460, September 1939.

48. Doctors in Other Fields., Southern Medicine and Surgery, 101: 619-622, December 1939.

49. Doctors Who Served Outside Limits of Medical Science., Bulletin Medical Association, 18: 46-53, July 1929.

50. Early Medical Men in the Northwest Who Were Naturalists., Western Journal Surgery, 51: 210-221, May 1942.

51. Encyclopedia Britannica, University of Chicago Edition.

52. Ernest Weinfeld, II, Medical Poets., Annals of Internal Medicine, 3: 1278-1287, June 1930.

53. Francisco Lopez de Villalbos, Spanish Court Physician and Poet., Bulletin Historical Medicine, 7: 1129-1139, December 1939.

54. History of Medicine., W. B. Saunders, Philadelphia, 1929.

55. James Rush, Dramatist., Quarterly Journal of Speech, 29: 55-61, February 1943.

56. John Hutchinson Gardiner, Canadian Naturalist and Physician., Canadian Medical Association Journal, 29: 314-316, September 1933.

57. Joseph Rodman Drake, Physician and Poet., Annals Internal Medicine, 2: 822-826, February 1929.

58. Journal American Medical Association, 156: 16, 36-38.

59. Journal American Medical Association, 156: 17, 1547-1549.

60. Life Magazine, 105-106, November 22nd, 1954.

61. Life of Omar Kayyami, J. K. Shirazi., A. C. McClurg & Co., Chicago 1910.

62. Literary Doctors., Canadian Journal of Medicine and Surgery, 65: 3, 77-82, March 1929.

63. Literary Doctors, Quarterly Bulletin Northwestern University Medical School, 19: 142-150, 1945.

64. Literary Doctors of Medicine., American Journal of Obstetricians and Gynecologists, 18: 303-314, September 1929.

65. Literary Doctors of Medicine., Transactions of American Gynecologists Society, 54: 1-12, 1929.

66. Lyman Hall, Yale 1747: Connecticut Doctor Who Mixed Medicine and Politics in Georgia., Yale Journal Biology and Medicine, 10: 531-537, July 1938.

67. Medical Contributors to Literature., Bulletin Medical Library Association, 27: 191-207, March 1939.

68. Medical Journal and Records., Vol. 135, 1932.

69. Medical Library Association Bulletin, Vol. 18, 1929.

70. Medical Life., Vol. 36, 1929.

71. Medical Men and Literature., Medical Journal of Australia, 2: 729-735, December 1941.

72. Medical Men as Early American Geologists., Medical Life, 36: 137-144, February 1929.

73. Reference deleted.

74. Medical Men as Explorers., Medical Journal of Australia, 1: 21, 875-886, May 1938.

75. Medical Men as Musicians., Annals Internal Medicine, 3: 1046-1054, April 1930.

76. Medical Men as Novelists, Medical Journal of Australia, 1: 225-232, February 1931.

77. Medical Poet Laureate, Robert Bridges, M.D., Annals Internal Medicine, 10: 1028-1032, January 1937.

78. Medical Truants, Lancet, 1: 1254-1259, May 1936.

79. Medical Truants, New Zealand Medical Journal, 46: 169-177, June 1947.

80. Medical Men Who Have Attained Fame in Other Fields of Endeavor., Annals Internal Medicine, 6: 444-448, September 1932, 3: 1279-1287, June 1930.

81. Medicine and Ornithology., Medical Press, 217: 158-163, March 1947.

82. Medicine and Poetry: Being an account of the Sons of Aesculapius who have on occasions paid homage to the elder god Apollo., Canadian Medical Association Journal, 36: 73-79, January 1937, 35: 676-682, December 1936.

83. Merrill Moore., Bulletin of the Medical Library Association, 29: 199-201, June 1941.

84. Moulder of Clay and of Men—Tait McKenzie., Journal Bone and Joint Surgery, 30: 790, June 1948.

85. Oliver Wendell Holmes: Anatomist, Autocrat, Poet., New England Journal of Medicine, 215: 11, 493-496, September 1936.

86. Oliver Wendell Holmes and the Physician Poet., New England Journal of Medicine, 217: 618-621, October 1937.

87. Omar Kayyam and His Age, Otto Rothfeld, D. B. Taraporevala Sons & Company, Bombay 1922.

88. Omar Kayyam; His Rubaiyat, His Life, Times and Work., E. D. Ross, G. D. Putnam Son, Knickerbocker Press, MCM.

89. Physicians as Dramatists, Journal Michigan State Medical Society, 34: 362-369, June 1935.

90. Physicians Eminent in Literature., Medical Journal and Records, 135: 542-544, June 1932.

91. Poet of Flanders Fields., Annals Internal Medicine, 6: 1657-1662, June 1933.

92. Poet Physicians—An Anthology of Medical Poetry Written by Physicians, Mary Lou McDonough., C. G. Thomas, 1945.

93. Poetry and Physic., Annals Medical History, 8: 1-15, March 1926.

94. Poetry and Physic, Medical Record, 154: 236-241, September 1941.

95. Richard Bright, Traveller and Artist., Bulletin Historical Medicine, 8: 909-933, July 1940.

96. Robert Bridges, British Medical Journal, 2: 540, October 1944.

97. Robinson Jeffers: Poet Who Studied Medicine., Medical Journal and Records, 130: 535-539, November 1929.

98. Role Played by Physicians in Discovery of New World., Boston Medical and Surgical Journal, 194: 494-495, March 1926.

99. Seymour Hayden: Surgeon, Painter and Etcher., Surgery, 4: 132-138, April 1938.

100. Sherrington's Contributions to English Literature., McGill Medical Journal, 17: 17-22, February 1948.

101. Sir William Osler as Critic of the Nove., Medical Records, 148: 340-342, November 1938.

102. Southern Medical Journal, Vol. 32, 1939.

103. Sports Illustrated Magazine., Vol. 2, No. 1, January 3rd, 1955.

104. Surgeons Library—The Book Shelf—Billroth and Brahms., Rudolph Marx, M. D., Surgery, Gynecology and Obstetrics, 100: 1, 121-125, January 1955.

105. The Colonel (Fielding H. Garrison) Played the Piano., Bulletin Historical Medicine, 5: 358-368, April 1937.

106. The Columbia Encyclopedia, 2nd Edition, Columbia University Press.

107. The New Century Dictionary., Vol. 2, Appleton Century, New York—London, Biographical Names.

108. Theodore Billroth as Musician., Bulletin Medical Library Association, 25: 209-220, May 1937.

109. The Oxford Companion to English Literature, James D. Hart., Oxford University Press, New York, 2nd Edition.

110. The Oxford Companion to English Literature., Sir Paul Harvey, Oxford University Press, London, 3rd Edition, 1953.

111. The Readers Encyclopedia, William Rose Benet., Thomas Y. Crowell, New York 1948.

112. The Story of Civilization—Our Oriental Heritage, Vol. 1, Simon and Schuster, 1935.

113. Thomas Holley Chivers., Annals Medical History, 3: 391-393, July 1931.

114. Thomas Holley Chivers, M.D., "The Wild Mazeppa of Letters"., Annals Medical History, 6: 241-254, May 1934.

115. Thomas Lodge—Doctor of Physik., Yale Journal Biology and Medicine, 7: 499-513, July 1935.

116. Webster New International Dictionary, Merrian Co., Springfield, Massachusetts.

117. Websters Biographical Dictionary., Merriam Company., 1943.

118. Whats New—Abbott Laboratories., Marion Mill Preminger, 12, December 1954.

119. Who Was Who in America., 1950.

120. Why We Became Doctors., Noah D. Fabricant, M. D., Grune & Stratton, New York 1954.

121. William Allen Pusey—Historian and Literateur., Archives of Dermatology and Syphilology, 35: 14-18, January 1937.

122. William Savage Pitts—A Medical Poet of the Middle Border., Annals Internal Medicine, 6: 52-58, January 1933.

123. World Telegram Almanac., 1953.

124. You Chan Yang—Korean Ambassador to the United States., Current Biography, 663, 1953.

A Simplified and Rapid Anatomical Approach to Parotidectomy

E. S. BRINTNALL, M.D.
R. T. TIDRICK, M.D.
and
W. C. HUFFMAN, M.D., Iowa City

There is a continuing controversy concerning the types of parotid gland tumors that may be adequately treated by enucleation or partial parotidectomy and those that require complete removal of the parotid gland with preservation of the facial nerve and its branches. Inasmuch as the parotid gland may be sacrificed with no physiological loss to the patient, the entire problem concerned in total parotidectomy consists of preservation of function of the facial nerve. As recurrence of mixed tumor is frequent after partial parotidectomy, total removal is indicated in all instances provided that the surgeon is able to rapidly locate and certainly preserve the facial nerve and its branches. The technique to be described has impressed us as being a safe and rapid method of preservation of the nerve in benign parotid tumors, and we now routinely perform total parotidectomies upon all patients in whom a parotid tumor exists. If an infiltrating malignant tumor is found, the facial nerve is sacrificed and a radical neck dissection is performed.

Submitted for publication April 25, 1955.

Read at the Twelfth Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Departments of Surgery and Otolaryngology, State University of Iowa, College of Medicine, and Surgical Service, Veterans Administration Hospital.

OPERATIVE TECHNIQUE

Incision.—Usually a vertical incision is begun above and in front of the tragus, carried downward to the ear lobe, then curved posteriorly in a curve which is turned anteriorly beneath the mandible in a skin crease.[1] Figure 2 illustrates the incision. At times a Y-incision [3] is used, but generally we avoid this because of occasional instances of impaired wound healing at the Y just below the ear lobe. Skin flaps are developed to uncover the parotid gland, and the anterior flap is sutured onto the face.

Locating the Trunk of the Facial Nerve.—Dissection proceeds deeply in the zone behind the parotid gland and close to the cartilaginous ear canal. The dissection hugs the canal until two bony prominences become easily palpable. These prominences are (*a*) superiorly, the sharp, fingernail-like bony ridge at the anteroinferior margin of the external auditory meatus of the skull, and (*b*) inferiorly, the broad blunt anterior margin of the mastoid process of the temporal bone. There is a V-shaped sulcus between these two bony landmarks, and in this sulcus the main trunk of the nerve is found (Fig. 1). The styloid process of the temporal bone lies deep and anterior and need not be located (it is sometimes absent) in order to find the nerve. When the sulcus is reached, the nerve cannot be more than 2 to 3 mm. from the depth of the dissection, and it can thus easily be identified either with or without a nerve stimulator. By utilization of this approach and these bony landmarks, the trunk of the facial nerve is routinely found within five

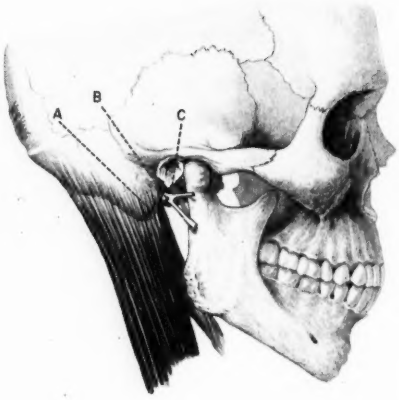


Fig. 1.—Diagrammatic illustration of the two bony landmarks utilized to locate the "palpable sulcus" in which the trunk of the facial nerve is found. *A*, blunt anterior surface of mastoid process; *B*, facial nerve trunk; *C*, sharp lateral margin of tympanic plate.

minutes of developing the skin incision.[2] The trunk is firm, of moderate size, and lighter in color than the surrounding fibrous tissue, and its recognition has not been difficult.

It has rarely been necessary to resort to the tedious tracing of a facial nerve branch backward to the main trunk because of location of a tumor.*

Removal of the Superficial Lobe: As the facial nerve enters parotid substance, it divides into upper and lower divisions, which course respectively above and below the isthmus connecting superficial and deep lobes of the gland.[2] Each division divides into branches which are sandwiched between the large superficial and the small deep lobe of the gland. A curved hemostat is inserted to follow superficial to each division and branch of the nerve; spreading the hemostat lifts the superficial lobe from the underlying nerve branches. Usually this lobe is removed by morcellation, by cutting down through gland over the course of each division of the facial nerve (Fig. 3). This serves to keep the nerve divisions in view as they are traced forward. Except in the case of very large tumors of the superficial lobe, this technique ordinarily does not involve incising through tumor. In case tumor is cut into or ruptured in the removal, care is taken to thoroughly rinse the operative area with saline before closing the wound. Stensen's duct, located at the anterior

Fig. 3.—The facial nerve enters gland between deep and superficial lobes. Nerve branches are exposed by incising through superficial lobe. (Drawn from photograph.)

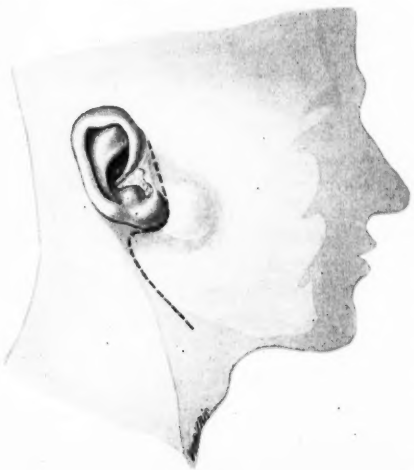


Fig. 2.—Curved cervico-facial incision utilized for parotidectomy.

* References 1, 3, and 4.

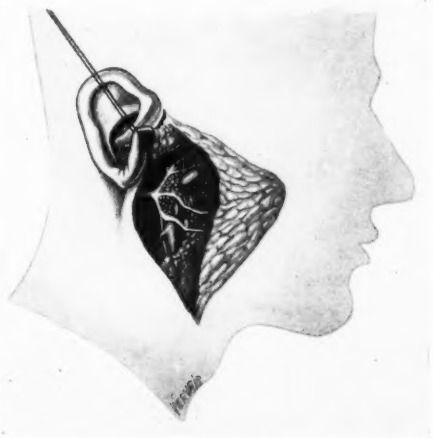


Fig. 4.—The superficial lobe of parotid has been excised. The small deep lobe lies beneath facial nerve branches. (Drawn from photograph.)

margin of the superficial lobe, is ligated and divided in conjunction with removal of the superficial lobe.

Removal of the Deep Lobe.—After the large superficial lobe has been removed, the small, retromandibular, deep lobe is removed piecemeal from between divisions of the facial nerve (Figs. 4 and 5). Care must be taken to avoid tearing the terminal portion of the external carotid artery and its branches and the large venous tributaries that lie within the deep lobe. This lobe is seldom involved except in the case of malignant tumors. If there is gross evidence of invasion of nerve or other structures adjacent to the parotid gland, a frozen section is studied. If malignancy is established, a radical en bloc removal of the gland to include the nerve is performed and a supraomohyoid neck dissection is added to the procedure.

A Penrose drain is inserted into the wound at the termination of the operation and is removed after 48 to 72 hours. The total operating time required for total parotidectomy with preservation of the facial nerve is often no more than one and one-half to two hours.

Temporary partial facial weakness (usually of the lower division) and occasional temporary complete facial weakness have been encountered frequently but have not constituted a problem. Usually recovery of facial nerve function occurs within a few days or weeks. Occasionally several months are required. Permanent loss of function in the lower division has occurred in instances in which this division was injured in previous surgery or in which it was intentionally sacrificed because of recurrent tumor involving it. There has been loss of function neither of an upper division nor of a complete nerve in 18 total parotidectomies or in 18 superficial lobe parotidectomies performed during the past five years. The nerve was sacrificed intentionally in four instances of malignant parotid tumors.

Our satisfaction with this technique for preservation of the facial nerve is leading us to abandon enucleations and limited excisions in favor of total parotidectomy. At the present time we routinely advise removal of the entire gland for benign lesions. The frequency of recurrence of mixed tumor in our own experience and in that of others would indicate that anything less than total parotidectomy is inadvisable provided the surgeon is able to save the function of the facial nerve with certainty and is not faced with an unduly tedious and prolonged operation in order to accomplish it.

Fig. 5.—Piecemeal removal of deep parotid lobe has been accomplished. The facial nerve branches lie superficial to the posterior facial vein. (Drawn from photograph.)

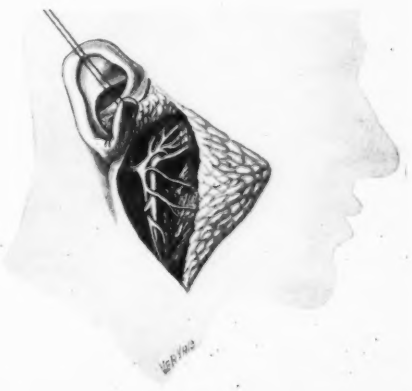


TABLE 1.—*Classification of Lesions in Sixty Patients*

Benign tumors		37
Primary mixed tumor	21	
Recurrent mixed tumor	8	
Adenolymphoma	4	
Mikulicz disease	1	
Parotid cyst	1	
Adenoma	1	
Unclassified	1	
Malignant tumors		17
Adenocarcinoma	9	
Carcinoma	4	
Malignant melanoma	3	
Reticulum cell sarcoma	1	
Inflammations		7
Actinomycosis	2	
Tuberculosis	1	
Chronic suladenitis	1	
Traumatic lesions		2
Fistula and upper division palsy	1	
Hematoma	1	

CLINICAL OBSERVATIONS

At the University Hospital and the Veterans Administration Hospital, Iowa City, 60 patients have been seen with "surgical" lesions of the parotid gland during the past five years; 62 operations were performed upon these patients. The lesions encountered are indicated in Table 1. It is of interest to note that 8 of 29 benign mixed tumors were recurrences after enucleation or partial lobectomy. In several instances the patients were seen because of second or third recurrences. It is not known whether recurrent mixed tumor represents residual tumor, a multicentric origin, or a response to trauma to the gland. Two of the carcinomas were thought by the pathologist to represent "malignant mixed tumor." One of these carcinomas represented malignant change occurring in a second recurrence of mixed tumor, nodules having been locally excised previously on two occasions, the second excision being performed 10 to 15 years prior to the last admission (L. H.). In a third patient with carcinoma, a history was obtained of a parotid nodule of 35 years' duration. It is believed that this carcinoma also originated from mixed tumor.

In two patients parotid enlargement was due to metastatic malignant melanoma to a lymph node within gland substance. These patients had previously had regional melanotic lesions excised. In one patient malignant melanoma was found within parotid substance and there was no evident primary lesion elsewhere and no history suggesting that a primary lesion might have existed at one time.

Our concern with the frequency of recurrence of mixed tumor after limited excisions and our concern with the possibility of malignant change in a mixed tumor and our satisfaction with the results of "radical" excisions of parotid tissue is reflected in Table 2, which indicates percentagewise the trend here toward total parotidectomy.

Superficial lobectomy should be the least radical procedure performed by a competent surgeon. Completion of the procedure by morcellation of the small deep lobe entails no additional risk to the facial nerve and has the advantage of leaving no parotid tissue to be the source of recurrence or of wound drainage of parotid secretion.

Gustatory sweating rarely appeared in patients following parotidectomy. It is probable that this phenomenon, when it does occur, is

TABLE 2.—*"Radical" Parotid Procedures* *

	1950	1951	1952	1953	1954
Total removal (nerve sacrificed)	0	0	0	2	2
Total removal (nerve preserved)	1	1	1	7	8
Superficial lobe lobectomy	1	1	1	10	1
	2 (33%)	2 (33%)	2 (50%)	19 (66%)	11 (69%)

* The tendency toward more radical extirpations is indicated percentagewise by the year-by-year tabulation.

due to trauma to the auriculotemporal nerve. Complete regression is to be expected within a few weeks and should not be confused with salivary fistula.

SUMMARY AND CONCLUSIONS

1. It is recommended that total parotidectomy be adopted as the routine surgical procedure for parotid tumors. The facial nerve and its branches need not be sacrificed for benign lesions.

2. Bony landmarks which indicate the position of the main trunk of the facial nerve permit rapid exposure of the trunk and, consequently, easy and rapid removal of the parotid gland without loss of facial nerve function. This anatomic approach is expedited by a combined facial-cervical incision of adequate type.

TABLE 3.—*Type of Operation Performed for Parotid Lesions*

	1950	1951	1952	1953	1954
Total removal (nerve sacrificed)	0	0	0	*2	*2
Total removal (nerve preserved)	1	1	1	7	8
Superficial lobectomy	1	1	1	10	1
Partial lobectomy	2	4	1	7	5
Enucleation	1	0	0	3	0
Biopsy	1	0	1	0	0
Totals	6	6	4	29	16

* In each of these patients "radical" parotidectomy with sacrifice of the seventh nerve followed superficial lobectomy because adenocarcinoma was found on histologic examination.

DISCUSSION

DR. F. G. KERGIN, Toronto, Canada: I wish to discuss Dr. Brintnall's paper, in which I am very interested. I am glad he has once again drawn attention to the very important contribution made a good many years ago by Dr. Robert Janes.

That contribution involved a method of demonstrating the facial nerve and was first published in the *Canadian Medical Association Journal* in 1940 and again in the *Surgical Clinics of North America* in 1943.

My own experience dates back to the early days when Dr. Janes first evolved this method, 18 years ago, and since that time I have used this method of demonstrating the nerve in all patients on whom I have operated for tumors of the parotid gland.

I believe we agree essentially with Dr. Brintnall that certainly no patient should ever have enucleation of any part of the parotid gland for tumor, but in all cases the nerve should be completely demonstrated. The method which he described this morning is much the easiest and safest method of exposing that nerve.

I am not sure that we deal with the superficial lobe in exactly the same way. We have been able to reflect the superficial lobe forward along the plane of the nerve as an intact lobe rather than dividing into it to follow the individual branches, and that seems desirable in tumor surgery.

Also, we do not agree that in all patients who have a benign mixed tumor it is necessary to remove all portions of the gland. We have been content to expose the nerve, reflect the lobe forward, and remove the tumor surrounded by an adequate amount of what appears to be normal gland. However, in those cases where we do wish to remove the deep portion (and usually they are malignant cases), we have been able to free the nerve and then, by working between the branches and around the nerve, remove the deep portion intact as a lobe, rather than by a fragmentary removal.

We do not agree that every patient who has malignant tumor should have the nerve sacrificed. We do so only if the main trunk is directly invaded. Quite often we find that we do sacrifice a branch of the nerve which is involved in the tumor and that produces very little deformity.

Finally, we do not do a block dissection of the neck in all cases of malignant parotid tumor. We reserve that procedure for those patients who have clinical evidence of involvement of the nodes of the neck or who develop that evidence later.

Dr. Janes has maintained a follow-up over the past 20 years of these cases treated in the Toronto General Hospital, and he gives me these figures: There have been 32 patients operated on for carcinoma of the gland, and 89 benign tumors developed evidence of recurrence during the period of follow-up. I am afraid I don't have the figures for the carcinomas.

DR. E. S. BRINTNALL, Iowa City: I wish to thank Dr. Kergin for his comments on my paper.

We are able as a routine, with the method we have described, to remove the gland within a couple of hours, usually an hour and a quarter or an hour and a half, and we are able to find the nerve trunk, once the skin flap is dissected, within five minutes. We feel this allows us to use the procedure quite widely.

I have no comment on removal of the deep lobe when it is not diseased, except that I am somewhat afraid to leave the tissue there, and there seems to be no additional hazard in removing it.

As far as cutting across the superficial lobe is concerned, I really don't believe it is harmful. I don't believe that recurrence of the benign mixed tumor will occur if one cuts across the gland to one side or the other of the tumor itself.

REFERENCES

1. Byars, L. T.: Preservation of the Facial Nerve in Operations for Benign Conditions of the Parotid Area, Ann. Surg. **136**:414-421, 1952.

2. Janes, R. M.: Surgical Treatment of Tumors of the Salivary Glands, S. Clin. North America **23**:1429-1439, 1943.

3. Martin, H.: The Operative Removal of Tumors of the Parotid Salivary Gland, Surgery **31**:670-682, 1952.

4. Riessner, D.: Surgical Procedure in Tumors of Parotid Gland, A. M. A. Arch. Surg. **65**:831-848, 1952.

Bilateral Sialoangiectasis of Parotid Glands

Report of a Case

J. DEWEY BISGARD, M.D.
and
KENNETH KIMBALL, M.D., Omaha

The term sialoangiectasis refers to a rather unusual condition of the salivary glands, characterized by gross cystic dilatation of the ducts and alveoli, a term used without reference to etiology. From a review of the literature, we were able to assemble only 15 cases. Of these, five were bilateral. The dilatation occurs without demonstrable obstruction of Stensen's duct. It, therefore, represents an entity not to be confused with the dilatation of the ducts which may occur with obstruction from calculi, stricture, or tumor. Sialoangiectasis is commoner in females and usually appears in middle life. It is occasionally preceded in onset by an upper respiratory infection and is characterized by pain and enlargement of one or both parotid glands. Occasionally, the submaxillary gland is involved. In most instances the painful swelling, often aggravated by eating, has recurred periodically over a period of months or years.

The etiology has been attributed to chronic inflammation by most pathologists, but Bailey discussed two cases which he believed to be congenital. Godwin has found sialoangiectasis in two cases associated with pathological changes which he described under the term, "benign lymphoepithelial lesion of the parotid," a condition which he believed to be inflammatory in character. This condition has been described by other authors under the terms adenolymphoma, chronic inflammation, lymphoepithelioma, lymphocystic tumor, and Mikulicz disease.

Fig. 1.—X-rays of injected parotids reveals saccular dilatation in both glands. Note the acute angulation present in Stensen's duct on the right 0.5 cm. from the buccal orifice.

Godwin, who has made an exhaustive study of this lesion, describes the pathological findings as (1) scattered foci, (2) diffuse involvement, (3) localized but nonencapsulated lesions, and (4) localized lesions with encapsulation. He states that the encapsulated type has the appearance of a neoplasm or hamartoma, while the remaining types show the hyperplastic reactive manifestation that is unique to the parotid gland. Grossly, these lesions vary from what appears to be a distinct tumor to a diffuse process. The lobular pattern of the gland is usually retained even in the diffuse form

Submitted for publication April 25, 1955.

Read at the Twelfth Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

Fig. 2.—Left side, showing parotid gland. Irregularity is present in the proximal portion of Stensen's duct on the left.

of the disease. The masses are usually soft to palpation and have the typical appearance of lymphoid tissue on cut section.

Histologically, the lesion consists of a mass of lymphoid tissue containing scattered foci of epithelial cells which are traceable to ductal origin. Acini may be present. These appear to be easily damaged or destroyed. The lymphoid tissue may be diffuse and frequently contains germinal centers, presenting, at times, a picture suggestive of lymphosarcoma. The epithelium varies from well differentiated to solid foci of closely packed cells. In glands with encapsulated lesions, there is no abnormality in the surrounding tissue.

In addition to the two cases of benign lymphoepithelial lesions of the parotid with associated sialoangiectasis, Godwin has described nine cases which apparently showed no appreciable dilatation of the ducts and acini. The case which we are presenting is typical of his two cases of sialoangiectasis associated with benign lymphoepithelial lesions of the gland.

The presence of sialoangiectasis can be demonstrated by sialoangiograms, but the basic pathology can be established only by microscopic examination.

The differential diagnosis of this lesion includes such conditions as (1) papillary cystadenoma lymphomatosum, (2) mixed tumors, (3) Mikulicz syndrome, (4) parotid hypertrophy, (5) epidemic and nonspecific parotitis, (6) lymphangiomas, (7) hemangiomas, (8) ductal stricture, and (9) calculi. Although lymphoepithelial lesions are benign, local recurrences often occur after incomplete removal of the gland.

Treatment of the cases of benign lymphoepithelial lesions of the parotid, reported in the literature, has consisted of surgical excision alone or excision followed by x-ray therapy. It is impossible to determine with certainty how many of these were associated with sialoangiectasis. It is also impossible to determine how many cases reported, solely from the point of view of sialoangi-

Fig. 3.—Right side, showing parotid gland.

ectasis, had associated benign lymphoepithelial lesions. For these reasons, its is impossible to make a comparative evaluation of the results of x-ray treatment versus surgical excision. Irradiation was used effectively in the management of recurrences following surgical excision of benign lymphoepithelial lesions in the cases reported. However, there would seem to be some question of its effectiveness in curing sialoangiectasis per se.

It would appear from the recorded high incidence of recurrence following partial removal of the gland that the extent of excision should be total extirpation. Total extirpation can be accomplished without damage to the trunk of the facial nerve and its branches. In a few of the reported cases, the facial nerve had been sacrificed with removal of the parotid gland owing to a misconception that the tumor was a malignant one. For this reason, it would seem wise to establish the diagnosis by biopsy in all tumors of the parotid gland before proceeding with a radical excision. Since a temporary paralysis of the facial nerve usually follows total extirpation, it would also seem desirable to stage the operations in cases of bilateral disease with a sufficient interval to allow return of function before undertaking the second operation.

REPORT OF A CASE

A white married woman of 55 presented herself Oct. 17, 1950, for treatment of bilateral swellings at the angles of the jaw. The mass in the right parotid area first appeared seven years previously and gradually increased in size; the one on the left was discovered one year previously and it too had gradually enlarged.

Six months before she reported for treatment the swelling on the right suddenly increased and was associated with pain and a sense of deafness in the right ear. Temporary relief was obtained from needle aspiration of "dark fluid," as has been the case on several occasions since that time.

One month before presenting herself for treatment the mass on the left side also became painful and was relieved with drainage by incision.

At no time had the swelling or pain increased with the ingestion of food.

The family and past histories were noncontributory with the possible exception of mumps at 15 years of age, removal of the tonsils 6 years before she came in for treatment "for the swelling in front of the right ear," and radium treatment for menorrhagia 15 years before this visit.

Physical examination and routine laboratory studies revealed no pertinent abnormalities with the exception of moderate obestity and the large masses involving both parotid glands. The size, location, and distribution of the swellings appeared similar to those of mumps. The masses were firm, slightly tender, and semifluctuant, but not hard or fixed. On both sides there were small recent drainage scars.

Although bougies could be threaded into the ducts for a considerable distance, it was impossible to induce a flow of saliva from the ducts by the usual methods of stimulating salivation.

Approximately 4 cc. of dark yellow cloudy fluid was aspirated from the mass on the right side for study. The report follows.

"The total protein is 1.2 gm/100 cc. (1200 mg.%). The hemoglobin level was less than 1 mg/100 cc. and the ptyalin activity calculated in amylase units was 588 units. There are also about ten minute fragments of tissue. A smash preparation of one of these shows essentially normal gland type epithelium and a few fibroblasts.

"Microscopic: Sections of the material aspirated from the parotid show essentially normal parotid tissue, and also there are a few small papillae covered by tall columnar epithelium which contains multiple secretory vacuoles. This is characteristic for epithelium lining ducts in parotid glands. It is considerably taller than normal and is slightly more papillary. Some points of it cover dense collections of lymphocytes in which there are occasional lympoid germinal centers. The entire picture is suggestive of adenocystoma lymphomatosum."

After aspiration of the cyst, both Stensen's ducts were intubated and injected with 5 cc. of contrast medium alternately, and stereoscopic oblique and anterior-lateral x-ray projections revealed the following:

"1. Bilateral cystic and saccular sialoangiectasis, the main area of involvement on the right at the angle of the mandible and the main area on the left in the retroaural extension of the gland.

"2. Irregular narrowing and partial stenosis of proximal portion of left Stensen's duct at the anterior margin of the parotid gland.

"3. Acute angulation of right Stensen's duct approximately 0.5 cm. from the buccal orifice."

On Oct. 19, 1950, the entire right parotid gland was removed, being painstakingly dissected from the branches of the facial nerve with the aid of

Fig. 4.—Left side, showing injected parotid gland.

frequent use of electric stimulation to identify the branches. After operation there was almost complete loss of function of the facial nerve, but during the subsequent six months function gradually returned.

The patient was reluctant to have the operation on the left side and did not return until June 22, 1953, one week after a sudden increase in swelling of the left parotid with moderately severe pain in the left ear and through the left side of the face. She stated that some bloody fluid had been aspirated five days previously but that only temporary relief of pain followed.

Resection of the left parotid gland with preservation of the branches of the facial nerve was carried out. As occurred on the right side, there was an immediate loss of function of the facial nerve and subsequently a gradual return.

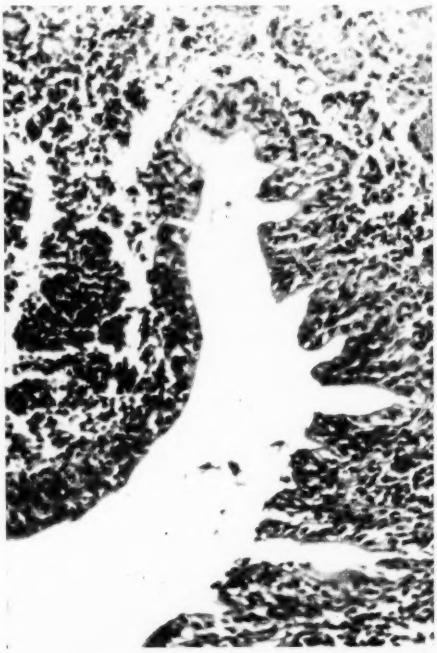
The gross and microscopic appearances of the two glands were essentially the same; hence the pathologists' description of the right gland will suffice for both.

"Gross: The specimen consisted of approximately 15 gm. of parotid tissue submitted in five separate sections, the largest being 40×20×5 mm. the smallest being 10×10×5 mm. The tissue is red, irregular, soft and on cut surface has several cystic areas approximately 5-10 mm. in diameter which contain a small amount of clear fluid.

"Microscopic: Sections show a number of dilated ducts and a little parotid tissue surrounding a large mass of lymphoid tissue in which there are well developed lymphoid germinal centers. Lymphatic channels are scattered through this mass. Many of them are dilated. The wall of the large cyst is composed of dense fibrous tissue lined by a thick layer of lymphoid tissue. The inner lining of the cyst consisted of poorly organized squamous type epithelium. This lesion has some of the characteristics of papaillary adenocystoma lymphomatosum except that its cysts are lined by squamous instead of columnar epithelium and there is considerably less epithelial hyperplasia than is usually present in the adenocystomas. The presence of a few fairly well developed and preserved parotid gland groups in lymph nodes is not too uncommon in the adenocystomas. The presence of a few fairly well developed and preserved parotid gland groups in lymph nodes is not too uncommon in the periparotid group of nodes. Recently, a series which described all stages in transition from simple glands in nodes to true papillary adenocystomas were described.

"Diagnosis: Congenital cystic dysplasia of parotid gland."

Fig. 5.—Photomicrograph. Note the cystic dilatation of duct, with thickening of duct wall in areas. There is marked lymphocytic infiltration present.



This case is reported as another example of benign lymphoepithelial lesion of the parotid gland associated with sialoangiectasis.

Now, two and five years after total extirpation of the two glands respectively, there has been complete relief of symptoms and no evidence of recurrence.

SUMMARY

Sialoangiectasis is a descriptive term for a gross pathological condition, the etiology of which is nonspecific.

It is the general opinion that this condition results from chronic inflammation.

The term benign lymphoepithelial lesion of the parotid gland has been advanced to describe the microscopic findings present in certain cases.

A case of this condition with bilateral sialoangiectasis is reported.

REFERENCES

1. Bailey, H.: Congenital Parotid Sialectasis, J. Internat. Coll. Surgeons. **8**:109-114, 1945.

2. Blady, J. V., and Hocker, A. F.: Application of Sialography in Non-Neoplastic Diseases of the Parotid Gland, Radiology **32**:131-141, 1939.

3. Carmichael, R.; Davie, T. B., and Stewart, M. J.: Adenolymphoma of the Salivary Glands, J. Path. & Bact. **40**:601-615, 1935.

4. Gaston, E. A., and Tedeschi, C. G.: Adenolymphoma of the Parotid and Submaxillary Glands, Ann. Surg. **123**:1075-1089, 1946.

5. Godwin, J. T.: Benign Lymphoepithelial Lesion of the Parotid Gland, Cancer **5**:1089-1102, 1952.

6. Heaton, T. G., and Shannon, E. H.: Mikulicz's Disease, Canad. M. A. J. **58**:368-370, 1948.

7. Hobbs, W. H., and Sneierson, H.: Infection of the Parotid Gland: Further Studies on Etiology and Treatment; Sialograms of Normal and Abnormal Glands and Ducts Including Tumors, Am. J. Surg. **32**:258-271, 1936.

8. Keith, H. M.: Infection of the Parotid Gland with Iodized Oil, J. A. M. A. **90**:1270-1271, 1928.

9. Lloyd, O. C.: Salivary Adenoma and Adenolymphoma, J. Path. & Bact. **58**:699-710, 1946.

10. Nash, L., and Morrison, L. F.: Asymptomatic Chronic Enlargement of the Parotid Glands: Review and Report of a Case, Ann. Otol., Rhin. & Laryng. **58**:646-664, 1949.

11. Plaut, J. A.: Adenolymphoma of the Parotid Gland, Ann. Surg. **116**:43-53, 1942.

12. Pyrah, L. N., and Allison, P. R.: Some Sialograms, Brit. M. J. **2**:1028-1030, 1931.

13. Swinburne, G.: Sialoangiectasis, Brit. J. Surg. **27**:713-716, 1940.

14. Swinton, N. W., and Warren, S.: Salivary Gland Tumors, Surg., Gynec. & Obst. **67**:424-435, 1938.

15. Wawro, N. W., and Fairweather, W.: Mikulicz's Disease of Parotid Glands; Report of a Case, Surgery **28**:767-770, 1950.

An Evaluation of Newer Methods in the Diagnosis of Hyperparathyroidism

B. E. BRUSH, M.D.
W. E. CHASE, M.D.
and
M. A. BLOCK, M.D., Detroit

Hyperparathyroidism is an uncommon disease. However, experience in the past 15 years clearly shows that it is commoner than previously realized and that physicians must be alert to think of its possibility. There are several important points to consider in this respect.

PROBLEMS IN THE DIAGNOSIS

1. The symptoms of the disease are not specific, and so, in general, the diagnosis of hyperparathyroidism is made in those patients showing two of the manifestations of the condition, namely, osteitis fibrosa cystica and renal lithiasis.

2. The osseous manifestations of the disease are relatively rare today in this country because our diet is high in calcium content. Therefore, most cases of hyperparathyroidism are now recognized by screening patients who have urinary lithiasis.

3. The diagnosis of hyperparathyroidism then requires laboratory confirmation in nearly all cases. In general, serum calcium and phosphorus determinations have been used in screening procedures, a level of serum calcium over 11 mg. per 100 cc. and a level of serum phosphorus under 3.5 mg. per 100 cc. usually being required for the diagnosis.

4. Several conditions produce variations in serum calcium and phosphorus levels, and so an erroneous diagnosis of hyperparathyroidism may be made. However, the greatest problem for the average physician lies in the difficulty of obtaining accurate and consistent determinations of phosphorus and, especially, of calcium.

The levels of serum calcium and phosphorus have remained the most important test in the diagnosis of hyperparathyroidism. Other tests are also utilized, but these have usually not provided information of greater diagnostic value. The finding of hypercalciuria has confirmatory value, but it occurs in many conditions and urinary calcium is elevated in a significant number of patients who have urinary lithiasis without hyperparathyroidism.[1] The basic or alkaline serum phosphatase merely reflects the degree of osseous changes associated with the condition and therefore is not definitive.

Other conditions which must be considered in the differential diagnosis of hyperparathyroidism include multiple myeloma, hypervitaminosis D, Paget's disease of bone, and sarcoidosis. In cases with bone changes the possibility of metastatic bone lesions must also be considered. The syndrome of severe renal damage with secondary hyperparathyroidism resembles primary hyperparathyroidism with secondary renal damage. These conditions are diffcult to differentiate and require the use of every available test.

We have been interested in tests which, although still requiring calcium and phosphorus determinations, utilize physiologic

Submitted for publication April 25, 1955.

From the Divisions of General Surgery and Urology, Henry Ford Hospital.

Read at the Twelfth Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

principles which may permit more definite establishment or rejection of the diagnosis of hyperparathyroidism.

A review was made of 52 cases seen at the Henry Ford Hospital in which the diagnosis of hyperparathyroidism was suspected. In 16 of the 52 patients there was evidence considered sufficient to warrant surgery, and a tumor was found in 14. Six of these patients have been reported previously by McClure and Lam.[2] In the remaining 36 patients complete studies finally resulted in a variety of diagnoses other than hyperparathyroidism, or for various reasons surgery was not carried out.

A study of the cases in which the diagnosis of hyperparathyroidism was questioned convinces one of the difficulty of definitely establishing or rejecting the diagnosis. In 11 of the group not operated on the values for serum calcium and phosphorus varied considerably, with a number of determinations definitely in the hyperparathyroid range. However, the evidence was not sufficient to advise surgical exploration. Several of this group are still under observation.

NEWER DIAGNOSTIC TESTS

Although our knowledge of the actions of the parathyroid hormone is incomplete and although there has been considerable controversy in the past with regard to its effect on the kidney, there now seems little doubt that a major function of the parathyroid hormone is to decrease renal reabsorption of inorganic phosphorus. Attempts have been made recently to utilize this principle in more definitive tests for the diagnosis of hyperparathyroidism.

Howard, Hopkins, and Connor[3] have described variations in the response of normal and hyperparathyroid persons to the intravenous administration of calcium salts. In normal persons, the intravenous administration of calcium salts in amounts sufficient to produce hypercalcemia results in a rise in serum phosphorus well over 1 mg. per 100 cc. and a reduction of 20 to 60% in urinary excretion of phosphorus. In patients with parathyroid adenomas the increase in serum phosphorus during the administration of calcium is less than 1 mg. per 100 cc. and the decrease in urinary phosphorus excretion is less than 20%, or a rise in phosphorus excretion may actually occur. The explanation for these findings is that hypercalcemia results in a "shutting-off" of parathyroid hormone secretion.* This "shutting-off" reaction is less marked in patients with hyperparathyroidism than in normal persons. These observations have been incorporated into an intravenous calcium tolerance test in which a saline solution containing a calcium salt is given at a constant rate over four hours so as to produce hypercalcemia. Blood for serum calcium and phosphorus determinations is taken before, at the midpoint, and at the end of the infusion, two to four hours after completion of the infusion, and 24 hours after the start of the infusion. Total 24 hour urine collections are taken during the day preceding the infusion and the day of the infusion. Although definite diagnostic criteria have not been established as yet, the diagnosis of hyperparathyroidism is highly suspected if the serum phosphorus fails to rise over 1 mg. per 100 cc. during the test and if the urinary excretion of phosphorus remains approximately the same as or is greater than the value obtained prior to the infusion of calcium.

The influence of parathyroid hormone on renal reabsorption of phosphorus has been utilized by Sirota,[5] and Schaaf and Kyle[6] as a diagnostic test for hyperparathyroidism. These investigators observed that renal phosphorus reabsorption was over 90% in normal persons, whereas it averaged 58% in three patients with hyperparathyroidism. The patients are placed on a diet containing moderate and constant amounts of calcium and phosphorus for three to five days. Fasting one- to four-hour urine specimens are then obtained and blood drawn midway in this collection period. Both blood and urine specimens are analyzed for phosphorus

* References 3 and 4.

and creatinine. By determining the endogenous creatinine clearance, the glomerular filtration rate is obtained. Then by using the values for the serum and urinary phosphorus levels, the renal reabsorption rate of phosphorus is calculated.

REPORT OF CASES

We have utilized the intravenous calcium tolerance test in four patients, three of whom underwent surgery. In two of the three patients operated upon, a parathyroid adenoma was found.

The first patient was a 59-year-old woman who came to the hospital in May, 1954, complaining of a cough of several months' duration and a dull headache. In 1930, a right renal calculus had been removed elsewhere. Her studies disclosed the presence of bilateral renal calculi with minimal function of the left kidney. Serum calcium levels were 11.8 and 12.5 mg. per 100 cc., and the phosphorus levels were 2 and 2.5 mg. per 100 cc. The serum proteins totaled 6.3 gm. per 100 cc. An intravenous calcium tolerance test was carried out (Figs. 1 and 2). In Figure 2 the data are shown in a more graphic form such as used by Howard, Hopkins, and Connor.[3] The serum phosphorus increased only 0.6 mg. per 100 cc., and the urinary excretion of phosphorus in the 24 hour test period decreased 31%. When the phosphorus value was corrected according to creatinine excretion, the phosphorus excretion remained essentially unchanged. This data being confirmatory, surgery was performed, and a chief-cell adenoma of the right lower parathyroid was removed. Postoperatively the serum calcium level remained below 9.7 mg. per 100 cc. The intravenous calcium tolerance test was repeated one week postoperatively. The serum phosphorus level now increased 2.0 mg. per 100 cc. and the urinary concentration of phosphorus decreased 74%, representing a normal response.

SPECIMEN	BEFORE SURGERY						AFTER SURGERY					
	SERUM		URINE (24 HRS)				SERUM		URINE (24 HRS)			
	CA (MGM %)	P (MGM %)	VOL (cc)	CREATININE (MGM)	CA (MGM)	P (MGM)	CA (MGM %)	P (MGM %)	VOL (cc)	CREATININE (MGM)	CA (MGM)	P (MGM)
CONTROL	12.4	3.0	1910	1460	376	754	8.7	2.6	1420	920	89	406
2 HR.	12.6	3.0					8.8	3.0				
4 HR.	20.8	3.1					12.3	4.4				
6 HR.	17.9	3.6					14.1	4.6				
24 HR.	12.5	3.1	2310	1010	702	514	10.1	4.0	1570	904	318	105

Fig. 1.—Effect of administration of intravenous calcium to patient with parathyroid adenoma (Case 1).

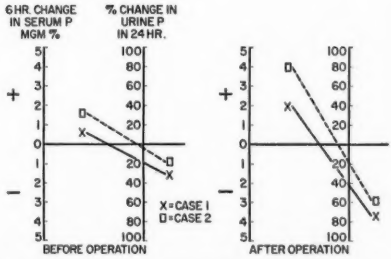


Fig. 2.—Serum and urine phosphorus response to intravenous calcium before and after removal of parathyroid adenoma. The serum phosphorus rise in milligrams per 100 cc. during the test is plotted to the left with the fall of urinary phosphorus in percentile variation from the control day plotted to the right. The two points are joined. Preoperatively the lines are nearly horizontal, whereas postoperatively they are nearly vertical.

The second patient was a 48-year-old woman who entered the hospital in 1954 because of bilateral flank pain present one week. She had experienced a similar episode of pain one year previously. Marked bilateral nephrocalcinosis was found during the course of her investigation. Her serum calcium levels ranged from 10.8 to 16.9 mg. per 100 cc., with serum phosphorus levels varying from 2.3 to 3.8 mg. per 100 cc. The values for the 24-hour determinations of urinary calcium were 54, 117, 166, and 292 mg. on different determinations. An intravenous calcium tolerance test was carried out (Figs. 2 and 3). The serum phosphorus concentration increased 1.6 mg. per 100 cc., which is somewhat greater than expected for a patient with hyperparathyroidism. However, the urinary excretion of phosphorus decreased only 19% and, after correction on the basis of creatinine excretion, actually increased. Thus, the presence of a parathyroid adenoma appeared likely, and an adenoma measuring 1.4×1.0×0.8 cm. was removed from the right lower position. Microscopically, it was

SPECIMEN	BEFORE SURGERY						AFTER SURGERY					
	SERUM		URINE (24 HRS)				SERUM		URINE (24 HRS)			
	CA (MGM %)	P (MGM %)	VOL (cc)	CREATININE (MGM)	CA (MGM)	P (MGM)	CA (MGM %)	P (MGM %)	VOL (cc)	CREATININE (MGM)	CA (MGM)	P (MGM)
CONTROL	14.0	3.0	2300	1190	292	968	9.6	1.8	1700	1070	40	485
2 HR.	13.6	2.8					13.8	3.0				
4 HR.	15.3	4.6					18.3	4.2				
6 HR.	21.7	4.6					16.3	5.8				
24 HR.	16.9	3.8	2530	708	374	784	11.1	4.0	30%	811	300	199

Fig. 3.—Effect of administration of intravenous calcium to patient with parathyroid adenoma (Case 2).

Fig. 4.—Right, parathyroid adenoma removed from Case 2. Left, photomicrograph of adenoma removed from Case 2 showing area of chief cells on the left and area of oxyphile cells on the right; hematoxylin and eosin; reduced about ⅔ from mag. × 90.

composed largely of oxyphile cells with some chief cells (Fig. 4). Postoperatively the intravenous calcium tolerance test was repeated. At this time the serum phosphorus increased 4.0 mg., which is a large increase. The urinary excretion of phosphorus decreased 59%, and, when corrected for creatinine excretion, decreased 46%. This was considered to be a normal response.

The third patient was a 39-year-old man who came to the hospital in 1954 complaining of recurrent renal colics with repeated passage of urinary stones since 1941. In 1948, a right nephrolithotomy had been carried out elsewhere. In 1951, a stone had been removed from the right ureter by manipulation. Studies disclosed the presence of bilateral renal calculi. The nonprotein nitrogen was 37 mg. per 100 cc.; the serum albumin was 5.0 gm. per 100 cc., with globulin 2.0 gm. per 100 cc. The serum calcium values varied from 11.3 to 13.1 mg. per 100 cc., with serum phosphorus values of 2.6 to 3.1 mg. per 100 cc. After being on a 150 mg. calcium diet for four days, the urinary calcium content was 361 and 288 mg. of calcium per 24 hours, indicating definite hypercalciuria. An intravenous calcium tolerance test was carried out (Fig. 5). The serum phosphorus increased 2.6 mg. per 100 cc., with a decrease in urinary phosphorus excretion of 21.9%. This was interpreted as probably a normal response. In view of the data other than the intravenous calcium tolerance test and the history of recurrent renal calculi, surgery was carried out and, finally, a suspected tumor 12×10×3 mm. on the left side posterior to the thyroid was removed. However, microscopically this was found to be composed largely of fat with

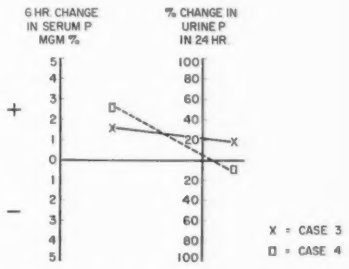


Fig. 5.—Serum and urine phosphorus response to intravenous calcium in other problem cases. The data are plotted as in Figure 2.

normal parathyroid tissue. Postoperatively the serum calcium has ranged from 10.3 to 11.0 mg. per 100 cc., with the serum phosphorus levels being 3.6 to 4.6 mg. per 100 cc. The hypercalciuria has persisted, being 242 and 303 mg. on two occasions. The negative intravenous calcium tolerance test proved to be correct in this instance.

The fourth patient was a 39-year-old man who came to the hospital in 1954 because of repeated episodes of fever, chills, hematuria, and flank pain since the age of 15. A stone in the left ureter had been removed by manipulation two and one-half years previously. The studies again disclosed the presence of stones in the left kidney. The nonprotein nitrogen was 29 mg. per 100 cc. The serum calcium was 10.0 and 10.7 mg. per 100 cc., with a serum phosphorus of 3.6 mg. per 100 cc. After the patient was on an Aub diet for four days, the urine calcium was 309 and 362 mg. in 24 hours, indicating marked hypercalciuria. The data thus are equivocal as far as the diagnosis of hyperparathyroidism is concerned. An intravenous calcium tolerance test was carried out (Fig. 5). The serum phosphorus increased 1.6 mg. per 100 cc., with a 19% increase in urinary phosphorus. There was an 88% reabsorption of phosphorus, by the phosphorus reabsorption test. The cumulative data were considered to mitigate against the diagnosis of hyperparathyroidism, and surgery has not been carried out.

Definite conclusions regarding the value of the calcium tolerance and the phosphorus reabsorption tests in the diagnosis of hyperparathyroidism cannot be made from the data accumulated to date. Heretofore, various diagnostic tests based on the determination of calcium excretion and phosphorus reabsorption have failed to be of real help in cases where other studies are equivocal. It has been necessary and likely will continue to be necessary to explore certain patients for a parathyroid tumor, even though the information is not definitely diagnostic.

COMMENT

The intravenous calcium tolerance test has proved of aid in the diagnosis of hyperparathyroidism. It is in the patient whose serum and urine calcium and phosphorus levels are equivocal that the test will be of most value, as in the third case presented. It seems unlikely that the test will be of great value in those cases where the problem is the differentiation of hyperparathyroidism secondary to severe renal damage, as in the Burnett syndrome.[7] Severe renal damage may so alter reabsorption of phosphorus by the kidney as to render the tests of limited value. Considerably more experience with these tests seems definitely desirable.

CONCLUSIONS

1. The positive diagnosis of primary hyperparathyroidism is at times very difficult.

2. The intravenous calcium tolerance test and the phosphorus reabsorption test give valuable information in suspected cases.

3. With further experience these tests may result in a higher percentage of positive preoperative diagnoses.

REFERENCES

1. Flocks, R. H.: Prophylaxis and Medical Management of Calcium Urolithiasis: The Role of the Quantity and Precipitability of the Urinary Calcium, J. Urol. **44**:183-190, 1940.

2. McClure, R. D., and Lam, C. R.: End-Results in the Treatment of Hyperparathyroidism, Ann. Surg. **12**:454-469, 1945.

3. Howard, J. E.; Hopkins, T. R., and Connor, T. B.: On Certain Physiologic Responses to Intravenous Injection of Calcium Salts into Normal, Hyperparathyroid, and Hypoparathyroid Persons, J. Clin. Endocrinol. **13**:1-19, 1953.

4. Clément, D.: Sur une méthode d'étude fonctionnelle des parathyroïdes, Presse méd. **62**:1170, 1954.

5. Sirota, J. M.: Renal Tubule Reabsorption of Phosphate in Hyperparathyroidism Before and After Removal of Parathyroid Adenoma, Fed. Proc. **12**:133, 1953.

6. Schaaf, M., and Kyle, L. H.: Measurement of per Cent Renal Phosphorus Reabsorption in the Diagnosis of Hyperparathyroidism, Am. J. M. Sc. **228**:262-268, 1954.

7. Burnett, C. H.; Commons, R. R.; Albright, F., and Howard, J. E.: Hypercalcemia Without Hypercalcuria or Hypophosphatemia, Calcinosis and Renal Insufficiency; a Syndrome Following Prolonged Intake of Milk and Alkali, New England J. Med. **240**:787-794, 1949.

Mediastinal Tumors of Thyroid Origin

J. L. EHRENHAFT, M.D.
and
JOSEPH A. BUCKWALTER, M.D., Iowa City

Masses of thyroid origin are usually confined to the cervical region. Extension into the retrosternal mediastinal space is not uncommon. The gland in these instances can be palpated in direct continuity with the substernal extension. There is usually no difficulty in diagnosis and surgical extirpation through the conventional cervical approach. This paper will concern itself only with masses of thyroid origin in which the main bulk of the tumor is located below the thoracic inlet and within the mediastinum. Confusion exists in the literature in regard to the differentiation of these two distinct groups of thyroid lesions. Therefore, the incidence of intrathoracic thyroid masses reported in the literature varies with the authors and their use and understanding of the terminology.* If the above criteria are adhered to,† the incidence of mediastinal goiters is stated to be about 1% to 2%.

Anatomic factors which play a role in the descent of thyroid adenomata into the mediastinum have been well described by other authors.‡ Most important is the arrangement of the prethyroid muscles and fascial planes which favor the descent of thyroid adenomata through the rigid thoracic inlet into the mediastinum. The final position of the intrathoracic mass depends on its site of origin from the thyroid gland and its relationship to the trachea and the major vessels. It is our opinion that the occurrence of mediastinal thyroid masses is principally on this basis. The presence of aberrant thyroid tissue which is seen rarely along the pathway of embryologic descent of the gland does not seem to be a reasonable explanation in most cases.§ Reports of isolated thyroid tissue in the mediastinum would seem to contradict this statement.‖ We have one patient in whom there was no demonstrable connection between the thyroid gland and the mediastinal goiter (Case 7).

At the State University of Iowa Hospitals, 13 patients with mediastinal masses of thyroid origin which satisfy the above requirements have been operated upon. In addition to these, we have seen at least an equal number of cases which we believe have intrathoracic thyroids in which operation has not been performed. Of the patients who have undergone surgery, 10 were women and 3 were men. The ages ranged from 37 to 67 years with an average of 54 years.

Previous thyroid surgery had been performed in four patients, two of whom had had two previous thyroidectomies. The indication for the original operation in three instances was thyrotoxicosis. It is of importance to note that the interval from the previous thyroidectomy to the discovery and removal of the mediastinal thyroid mass varied from 8 to 34 years. Two possible explanations may be offered, either failure to consider the possibility of an additional intrathoracic mass at the time of thyroidectomy or the development of the mediastinal mass during the interval. Occasional patients may have no, or only minimal, vague pressure symptoms, all of which can be explained on the basis of compression of the adjacent mediastinal struc-

Submitted for publication April 25, 1955.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Department of Surgery, State University of Iowa College of Medicine.

* References 1, 2, 8, 10, 12, and 13.

† References 2, 3, 4, 7, 8, and 12.

‡ References 6, 8, and 10.

§ References 3, 5, 6, 7, 8, 9, and 12.

‖ References 9 and 13.

TABLE 1.—*Symptoms of Patients*

Cough	8
Dyspnea	7
Pressure	6
Choking	4
Toxicity	3
Dysphagia	2

tures. In addition to these symptoms, we have seen patients with cough, choking, dyspnea, dysphagia, and symptoms of mild thyrotoxicosis. Hoarseness due to recurrent laryngeal involvement was not present in any of the patients. In Table 1 are listed the symptoms which were experienced by this group. These complaints ranged from 6 months' to 34 years' duration.

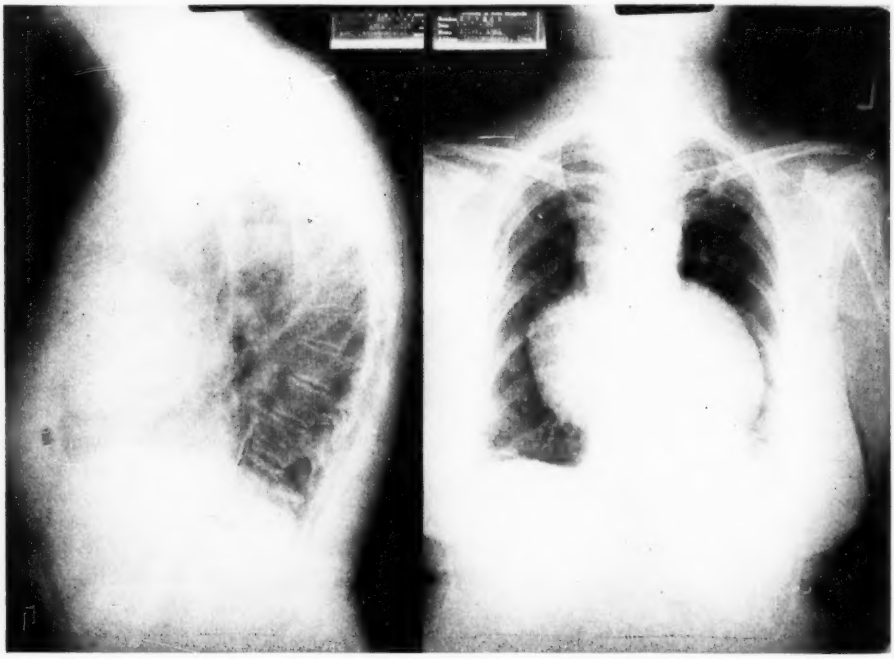
No palpable supraclavicular masses were noted in seven of our patients. In the remaining 6, small nodules in the neck or an ill-defined retrosternal mass was discernible. The presence of nodular cervical thyroid enlargement does seem to us to be of significance and is additional evidence in favor of a mediastinal goiter. A diffuse enlargement of the cervical gland with signs of hyperthyroidism argues against the presence of an intrathoracic goiter. The signs of superior vena cava compression in the form of dilated collateral superficial venous channels over the anterior chest wall were noted in two patients. They were found to have posterior mediastinal goiters. In addition, four patients had jugular vein stasis with dilated cervical veins. The three patients previously referred to had physical signs of mild thyrotoxicosis.

In Table 2 the various diagnostic studies completed are listed with an indication in how many cases they were helpful in establishing the preoperative diagnosis. In our opinion, the routine chest roentgenograms

TABLE 2.—*Diagnostic Studies Made*

	Done	Helpful
Routine roentgenography	13	13
Bronchoscopy	6	4
I^{131} survey	6	4
Bronchography	4	3
Esophagraphy	6	2
Planography	1	1

Fig. 1 (Case 6).—Anterior mediastinal goiter.



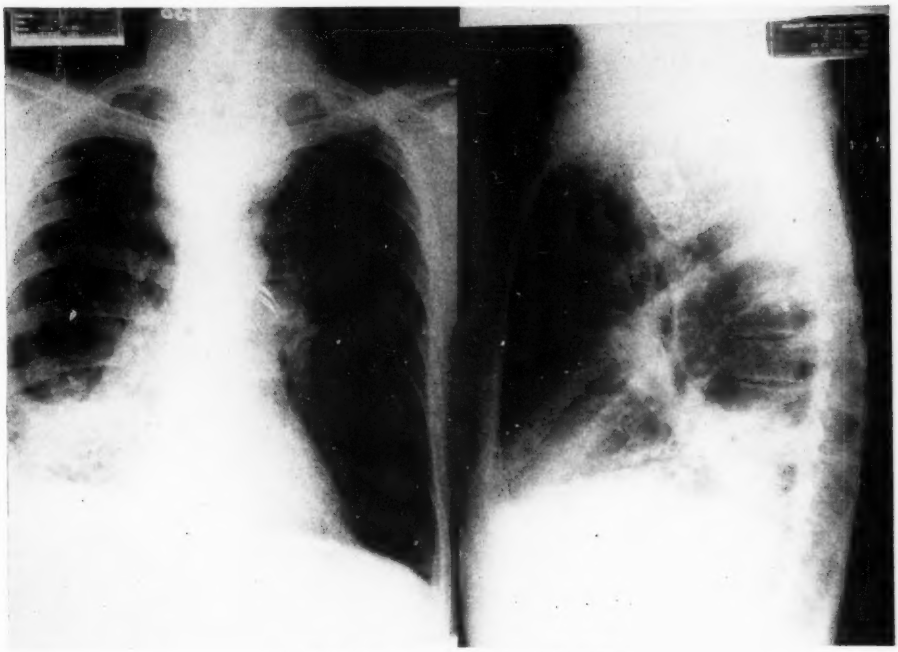
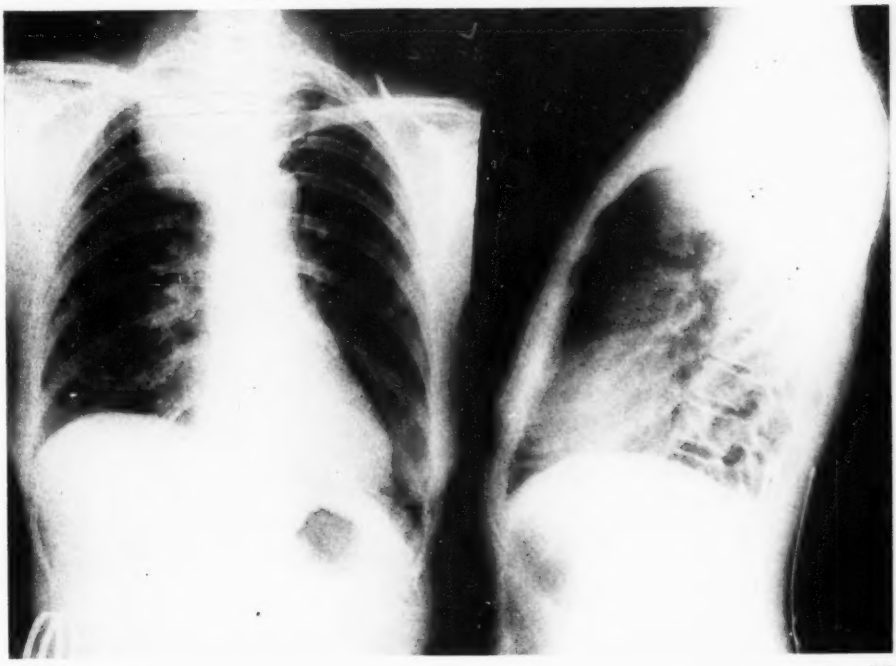


Fig. 2 (Case 10).—Midmediastinal goiter.

Fig. 3 (Case 2).—Posterior mediastinal goiter.



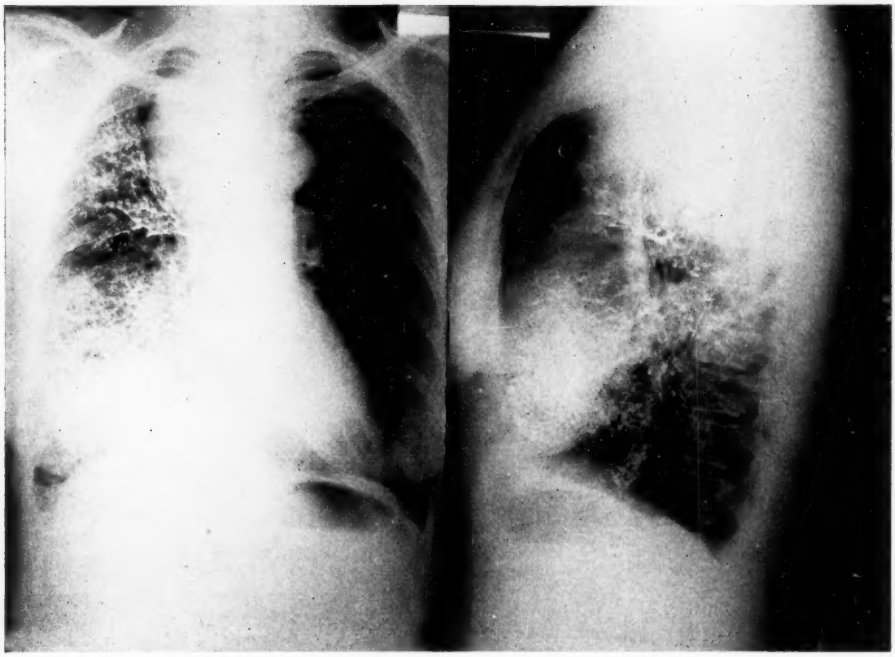
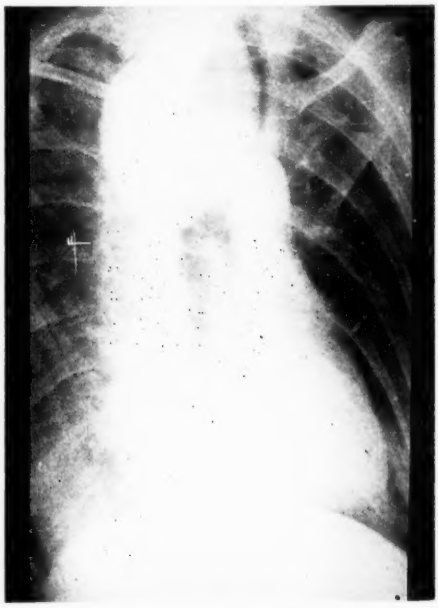


Fig. 4 (Case 9).—A posterior mediastinal goiter demonstrated by bronchography.

in the posteroanterior, lateral, and oblique projections are often diagnostic (Figs. 1, 2, and 3). Planography done in only one instance clearly demonstrated the position of the lesion (Fig. 8). Calcification in degenerated adenomata will be evident (Fig. 2). Fluoroscopy of the chest to demonstrate the relationship of the mediastinal mass to the trachea, esophagus, and large vessels was found to be of help in the differentiation from other mediastinal tumors. These examinations frequently demonstrated displacement or compression of the trachea and bronchi in a rather characteristic manner. Bronchography demonstrated in a few patients in which it was employed displacement of the surrounding pulmonary tissue and bronchial tree by the mass (Fig. 4). The pulmonary tissue could be distinguished as surrounding the mass but not being invaded by it. This is particularly true in midmediastinal and posterior mediastinal masses. Bronchography has little to offer in patients with an anterior mediastinal goiter. Esopha-

Fig. 5 (Case 1).—Posterior mediastinal goiter removed through cervical approach.



grams are of value only in those posterior mediastinal goiters in which there is extreme displacement of the esophagus. Occasionally, bronchoscopy will show displacement or compression of parts of the tracheobronchial tree. All the above-mentioned investigations if positive indicate the presence of a mediastinal mass, the nature of which is uncertain. As other authors have mentioned, the radioactive iodine survey provides the only possibility of making a definite diagnosis.¶ Since many of these intrathoracic goiters have undergone extensive degenerative changes as will be discussed later, they may take up little or no radioactive iodine, therefore making a specific diagnosis impossible.

The differential diagnoses in this group of patients included lymphoma, neurofibroma, dermoid, thoracic aorta aneurysm, thymoma, and carcinoma of the lung. The correct diagnosis was made preoperatively in 11 patients. It is interesting to note that two of the earlier patients included in this series were subjected to a course of external irradiation therapy with the presumptive diagnosis of mediastinal lymphoma. It is our opinion that the correct diagnosis can be made if the proper preoperative investigations are completed.

In two patients included in this study, large posterior mediastinal goiters were removed through a conventional thyroid incision (Figs. 3 and 5). The difficulties encountered included severe bleeding during the operative procedure and postoperatively in addition to incomplete removal of the intrathoracic goiter. The sternum-splitting incision was used in five instances. In two of these patients, the conventional thyroid incision was first made. When it became evident that it would be impossible to remove the goiter present in the anterior mediastinum, the sternum was split. In one patient in whom the sternum was first split it was necessary to extend the wound by a collar type of incision in order to remove additional adenomatous goiter in the cervical portion of the gland. Two patients had a sternum-splitting anterior mediastinotomy only. In the other six patients the mediastinal goiter was removed through a lateral thoracotomy incision. Unfortunately, in one of those patients (Case 8) the approach was through a left thoracotomy, which proved most unsatisfactory. Exposure of the mediastinal goiter was difficult and removal incomplete owing to the presence of the interposed mediastinal structures. This patient was the only one who had injury to a recurrent laryngeal nerve.

If a patient has an intrathoracic goiter which satisfies the criteria presented, it is our opinion that removal by the cervical approach alone is not indicated. The reasons are the difficulty in controlling hemorrhage, possible injury to recurrent laryngeal nerves, and, often, the impossibility of complete removal of the adenomatous goiter. The anterior mediastinal goiter should always be approached through a sternum-splitting incision. This becomes particularly important when, as occurred in two of our cases, the anterior mediastinal mass consisted of a left and a right component (Cases 5 and 6). Another advantage of this incision is the ease with which it can be extended into the neck, thus permitting removal of adenomata of the cervical portion of the gland. Intrathoracic goiters located in the mid and posterior mediastinum should nearly always be approached by a right lateral thoracotomy. Rare patients may be seen in whom a left-sided approach should be considered owing to the unusual location of the mass to the left of the mediastinal structures. Lateral thoracotomy and the sternum-splitting approach both have the distinct advantage of providing good access to the mediastinal tumors, which permits complete removal and accurate hemostasis. The one disadvantage of the lateral approach is the difficulty of removing additional neck masses during the same operative procedure. Five of our patients had posterior and three mid-mediastinal goiters, all of which anatomically were located either posterior to or to the right of the mediastinal structures and large vessels. The five other patients had substernal anterior mediastinal masses. All goiters had some connection with the thyroid gland in

¶ References 2, 4, and 11.

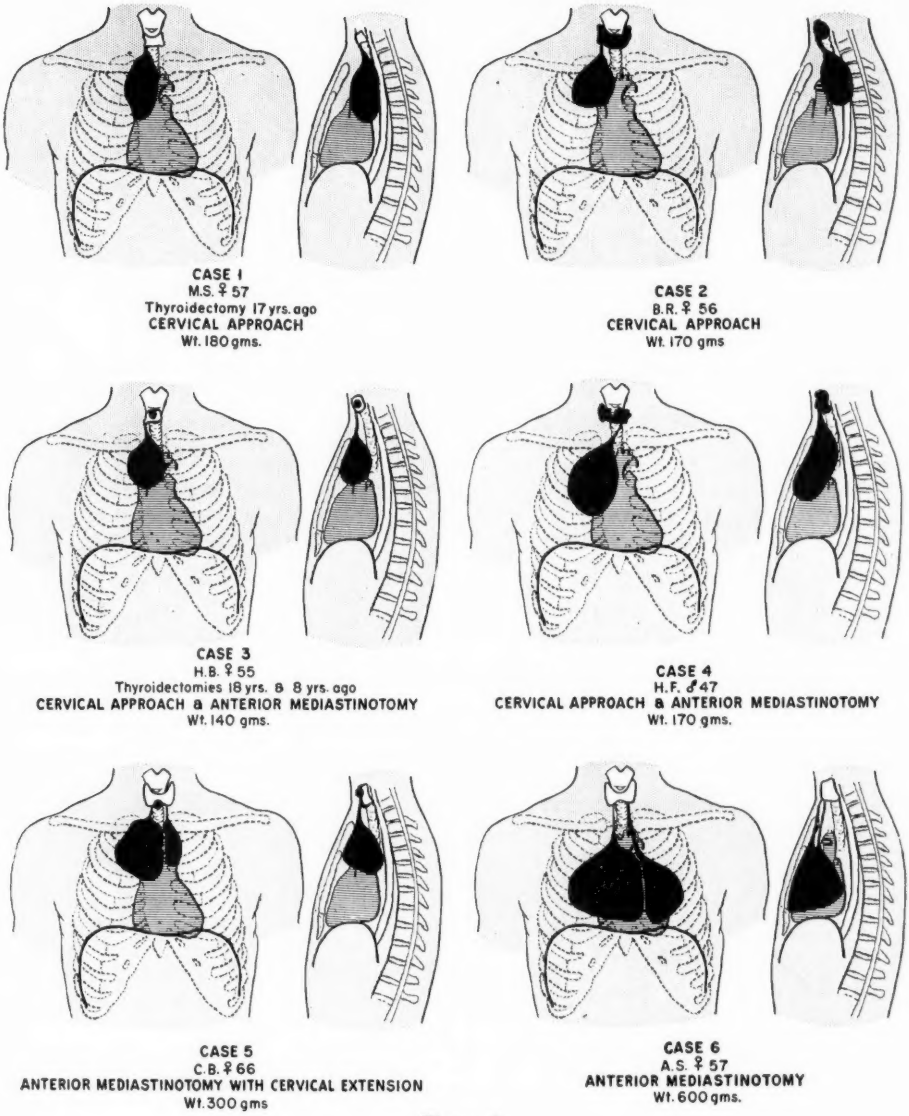


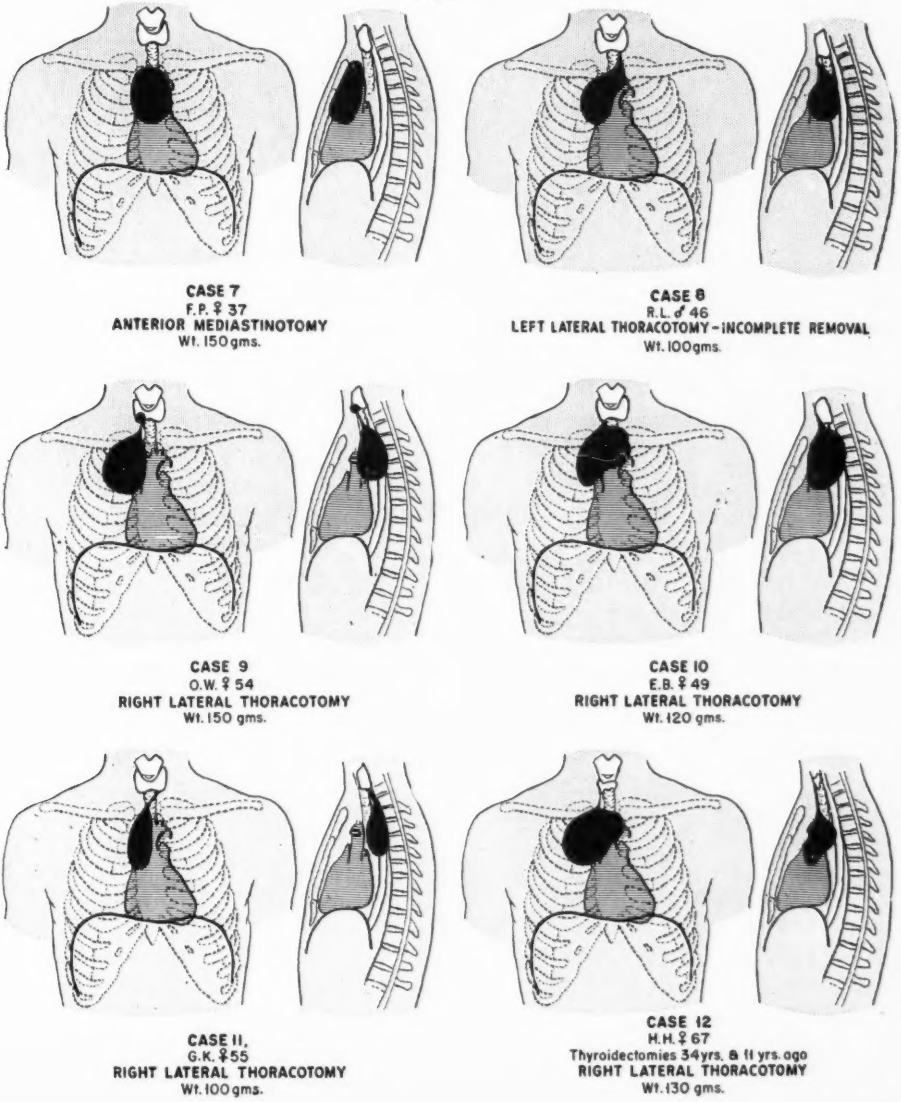
Figure 6

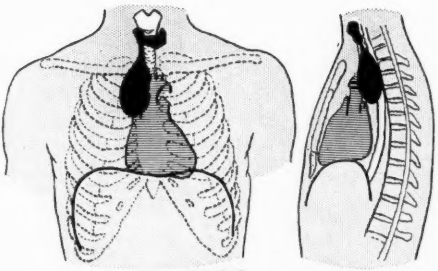
the form of narrow pedicles except one, which, as previously mentioned, was entirely separated. In three instances the attachment was to the left, in seven to the right, and in two there was attachment to both lobes of the cervical thyroid. It is interesting to note that two of three goiters attached to the left lobe of the cervical gland were located in the right posterior mediastinum. One of these was easily removed by right lateral thoracotomy. In the two cases with attachment to both lobes, the goiter was located in the anterior mediastinum. Figures 6, 7, and 8 show diagrammatically the location of the 13 mediastinal goiters and their attachments to the normal or abnormal cervical glands. The

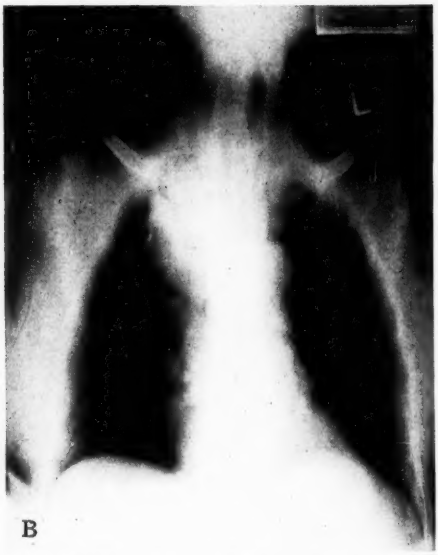
surgical approach employed and other pertinent data are indicated. In Figure 8 photographs of the operative findings of Case 13 are also shown. The often meager vascular supply of the intrathoracic mass is provided by the inferior thyroid arteries, which form part of the narrow pedicles, and by unnamed mediastinal vessels. The recurrent laryngeal nerve has never been visualized intrathoracically, inasmuch as its normal relations are not disturbed. Likewise, the parathyroid glands have not been noted, and no postoperative hypoparathyroidism has occurred.

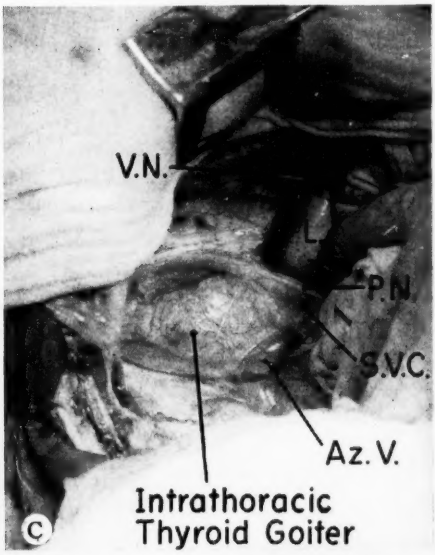
In two of our patients, postoperative myxedema developed (Cases 5 and 7). In one of those the preoperative survey demonstrated

Figure 7









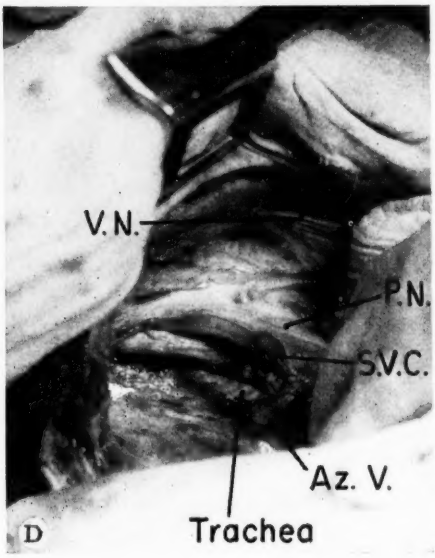


Fig. 8 (Case 13).—*A*, diagrammatic representation of position and attachments of posterior mediastinal goiter; *B*, planogram; *C*, at operation before removal of goiter; *D*, after removal of goiter.

substantial radioactive iodine uptake in the mediastinal area (Case 7). The classic symptoms and signs of severe thyrotoxicosis with thyrotoxic heart disease developed one month postoperatively in one patient who definitely appeared euthyroid prior to surgery and whose studies indicated a euthyroid state (Case 12). There have been no additional postoperative morbidities and no mortalities.

The gross appearance of the intrathoracic goiters was that of a multinodular, well-encapsulated mass sometimes quite adherent to adjacent mediastinal structures, particularly if they were located in the posterior mediastinum. The weights varied from 100 to 600 gm., the ones encountered in the anterior mediastinum being the largest. The degenerative changes in the mediastinal goiters seem to be more pronounced than similar changes encountered in cervical goiters. Microscopic sections showed the typical features of a colloid goiter in two instances

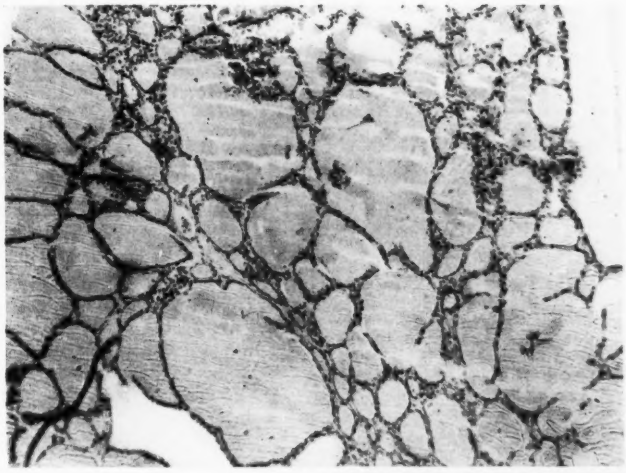


Fig. 9 (Case 1).—Colloid goiter-like findings; reduced to 3/5 of mag. × 150.

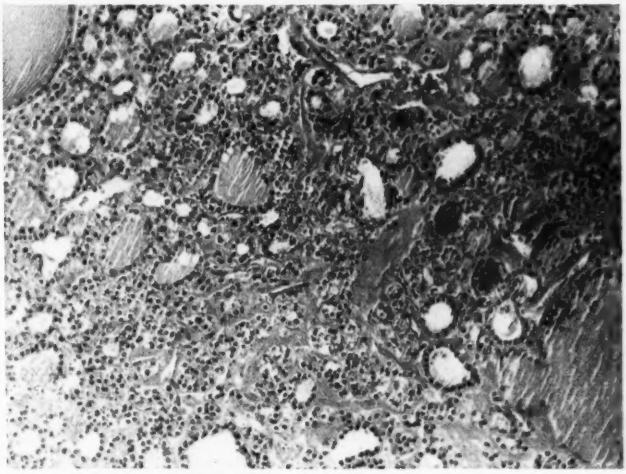


Fig. 10 (Case 8).—Fetal adenomatous changes; reduced to 3/5 of mag. × 150.

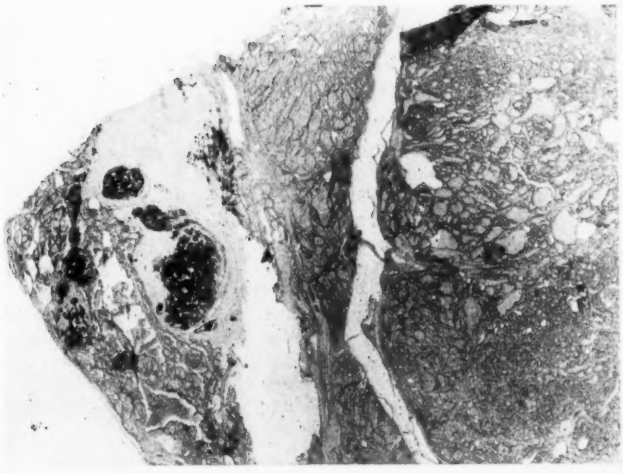


Fig. 11 (Case 4).—Typical changes of multinodular goiter; reduced to 3/5 of mag. × 10.

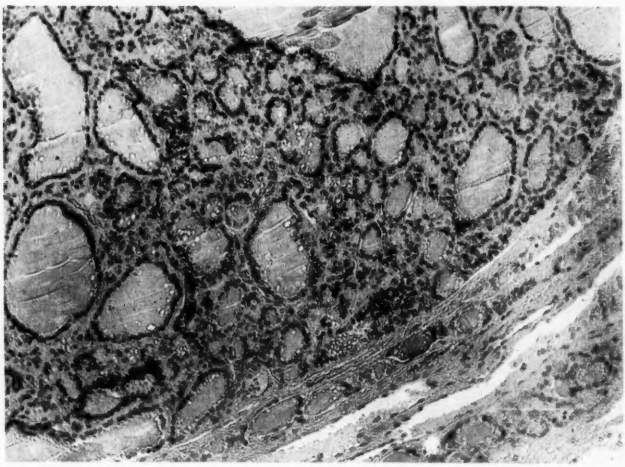


Fig. 12 (Case 2).—Areas of hyperplasia in nodular goiter; reduced to ⅜ of mag. × 150.

(Fig. 9) and fetal adenomatous changes in one (Fig. 10). The remaining 10 showed the various characteristics of typical multinodular goiters (Fig. 11). This includes areas of calcification, old hemorrhage, large dilated acini with flat epithelium, and an extensive amount of scarring. Focal areas of hyperplasia were noted in the goiters removed from two patients who had mild thyrotoxicosis (Fig. 12). The diffuse hyperplastic goiter has not been noted which is in agreement with observations of others.[6] Neoplastic changes were not present in our group of patients.

SUMMARY

Mediastinal masses of thyroid origin have been defined as those goiters whose main bulk is below the thoracic inlet. The signs and symptoms encountered in a group of 13 patients have been discussed. They resulted from the mechanical pressure exerted by the intrathoracic mass or the adjacent mediastinal structures. The available diagnostic methods have been discussed and have been illustrated. All of them are nonspecific except in the occasional patient in whom the radioactive survey shows a significant uptake in the mediastinum. The positions which these tumors have occupied have been demonstrated. Having the technical adavantages and the safety of the patients uppermost in mind, we prefer the anterior sternum-splitting thoracotomy for anterior mediastinal masses or the right lateral thoracotomy for mid and posterior mediastinal thyroid tumors.

REFERENCES

1. Adams, H. D.: Transthoracic Thyroidectomy, J. Thoracic Surg. **19**:741, 1950.

2. Bressler, S., and Thompson, S. A.: Posterior Mediastinal Goiter, Am. J. Surg. **85**:237, 1953.

3. Crile, G., Jr.: Intrathoracic Goiter, Cleveland Clin. Quart. **6**:313, 1939.

4. Ellis, F. H.; Good, C. A., and Seybold, W. S.: Intrathoracic Goiter, Ann. Surg. **135**:79, 1952.

5. Judd, E. S.: Intrathoracic Goiter, Internat. Clin. **1**:149, 1920.

6. Lahey, F. H., and Swinton, N. W.: Intrathoracic Goiter, Surg., Gynec. & Obst. **59**:627, 1934.

7. McCort, J. J.: Intrathoracic Goiter: Its Incidence, Symptomatology and Roentgen Diagnosis, Radiology **53**:227, 1949.

8. Pemberton, J.: Surgery of Substernal and Intrathoracic Goiters, Arch. Surg. **2**:1, 1921.

9. Rives, J. D.: Mediastinal Aberrant Goiter, Tr. Am. S. A. **65**:417, 1947.

10. Sweet, R. H.: Intrathoracic Goiter Located in the Posterior Mediastinum, Surg., Gynec. & Obst. **89**:57, 1949.

11. Touroff, A. S. W., in discussion of paper by Adams, H.: Transthoracic Thyroidectomy, J. Thoracic Surg. **19**:751, 1950.

12. Wakeley, C. P. G., and Mulvany, J. H.: Intrathoracic Goiter, Surg., Gynec. & Obst. **70**:702, 1940.

13. Wenzl, M.: Mediastinale und aberrante mediastinale Strumen, Wien klin. Wchnschr. **62**: 43, 81, 1950.

The Surgical Treatment of Retrotracheal Intrathoracic Goiter

ELMER R. MAURER, M.D., Cincinnati

Numerous surgical procedures have been suggested for the proper management of thyroid masses which migrate into or occur ectopically in areas removed from their usual anatomical location in front of the trachea. It is generally accepted that subclavicular and substernal extensions of moderate size are easily and properly delivered through the conventional cervical incision. Unusually large masses, if soft, can be reduced in size before delivery by the morcellation technique of Lahey.[1] Substernal extensions, however, which have migrated far inferiorly or are too solid to allow intracapsular "gouging" are best removed by using a combined cervical and median sternotomy approach.[2]

That thyroid tumors can occur ectopically is suggested by authentic reports of intratracheal, aortic, pericardial, and intracardiac accessory thyroid masses.* Some of these ectopic tumors have been encountered deep in the thorax above the diaphragm or in the posterior mediastinum behind the esophagus far removed from the cervical gland and with a vascular supply completely absent or derived from the local mediastinal vessels.[5] These totally intrathoracic goiters presenting entirely within the chest to either side of the midline are most easily removed through the conventional posterolateral thoracotomy incision.[6]

I have encountered an unusual if not unique variety of intrathoracic thyroids arising from the unilateral cervical lobe with extension behind the trachea and vena cava into the opposite hemithorax.

These descending enlargements of the thyroid gland through abnormal channels behind the trachea and great vessels with maintenance of the blood supply at a point of origin far removed in the neck exaggerated the technical hazards ordinarily involved in the removal of such tumors. This arrangement is exceedingly rare and presents unusual problems in surgical exposure, delivery of tumor, and control of blood supply.

The following two case reports will illustrate the important clinical findings and technical problems presented by this unusual type of intrathoracic goiter.

REPORT OF A CASE

CASE 1.—A 52-year-old white man was admitted to the hospital April 4, 1952, with a history of having had increasing pressure symptoms in the neck with dyspnea during the 10 years.

On physical examination the patient was markedly obese. Examination of the neck revealed enlargement of both lobes of the thyroid gland, particularly marked on the right. The heart was moderately enlarged to the left, and there was a systolic murmur audible at the apex. The blood pressure was 188/100. There were a right inguinal hernia and bilateral varicose veins. The B. M. R. was reported as +14%.

A. P. A. projection roentgenogram of the chest revealed a large mass in the right superior mediastinum protruding into the right upper thorax (Fig. 1). An unusual finding was the deviation of the trachea and esophagus to the same side as the mediastinal mass (Fig. 2). Under ordinary circumstances the trachea is deviated to the opposite side. This finding alone suggested that the mass probably arose in the neck and then descended across the midline, deviating the trachea in the same direction. A lateral projection roentgenogram of the chest showed the mediastinal mass to be located behind the trachea, which was dislocated anteriorly, and

Submitted for publication April 25, 1955.

From the Department of Surgery, University of Cincinnati College of Medicine and the Cincinnati General Hospital.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

* References 3 and 4.

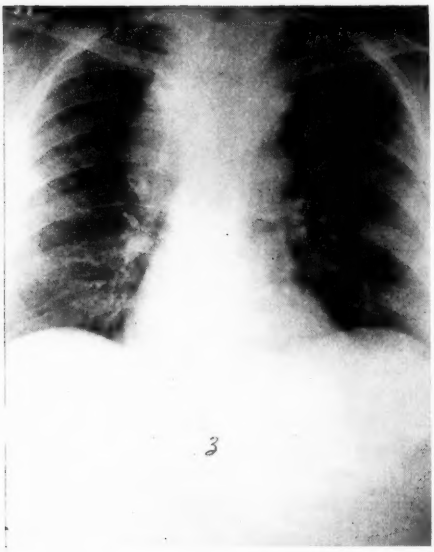


Fig. 1 (Case 1).—P. A. chest roentgenogram shows large tumor in right superior paramediastinum.

in front of the esophagus, which was displaced posteriorly (Fig. 3).

Because of the finding of a cervical tumor in association with roentgenographic evidence of a superior mediastinal mass and tracheal dislocation, a diagnosis of cervical goiter with retrotracheal extension across the mediastinum into the right thorax was made.

Operation (April 7, 1952).—Through the conventional collar incision a large adenomatous goiter arising from the right lateral lobe of the thyroid gland was exposed. The mass extended beneath the clavicle, but the inferior pole could be delivered completely, demonstrating that it had no relationship with the mediastinal portion of the tumor. Eighty-five per cent of the right lateral lobe was removed along with an enlarged isthmus. The inferior pole of the normal-appearing thyroid on the left side was then examined, and a very large mass was seen to arise from this area and extend behind the trachea across the midline deep into the chest. The superior pole vessels, which were rather large and elongated, were doubly ligated and divided; afterward the mass was freed from the surrounding structures. It was impossible to move the goiter by traction on the cervical protrusion.

Fig. 2 (Case 1).—P. A. roentgenogram shows dislocation of trachea and esophagus to same side as tumor.

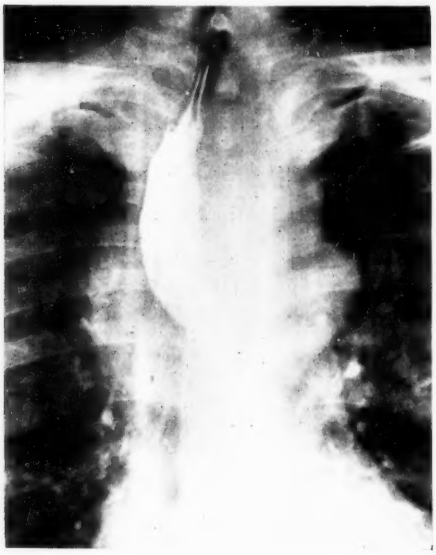


Fig. 3 (Case 1).—Lateral chest roentgenogram shows anterior displacement and compression of trachea and posterior dislocation of esophagus.

After closure of the cervical incision the patient was placed in the left lateral prone position and the right chest entered through the bed of the fifth rib, which was subperiosteally resected. The central portion of the superior mediastinum was completely occupied by a large, firm, elastic thyroid tumor measuring 8 by 7 by 5 cm. It displaced and compressed the trachea anteriorly and the

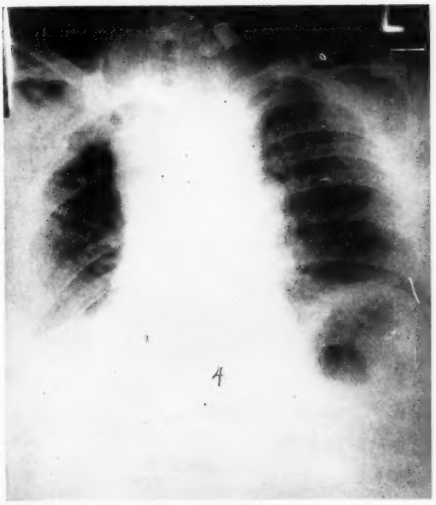


Fig. 4 (Case 1).—Postoperative portable roentgenogram of chest shows widened mediastinum and clear lung fields after bronchoscopy and tracheotomy.

esophagus posteriorly. The azygos vein was mobilized, doubly ligated and divided; after this the mediastinal pleura was opened widely over the tumor. The thyroid mass was dissected down to a fairly large pedicle which was seen to extend into the upper end of the thoracic inlet. The pedicle was ligated and the mass excised. Extensive dissection, however, high in the thoracic inlet was necessary before the thyroid tumor could be delivered, and, as a result of this, there was brisk bleeding from what appeared to be venous sinuses about the trachea and esophagus. This was controlled first with gauze packing followed by the instillation of oxidized Cellulose (Oxycel) gauze. The lung was reexpanded and the chest wall closed.

Postoperative Course.—On the day after surgery the patient developed signs of acute laryngeal obstruction and a tracheotomy was performed as an emergency measure. His condition immediately improved. On the second postoperative day the patient developed cyanosis and the pulse became rapid. Bronchoscopy yielded large quantities of thick mucus. This persisted despite adequate suction through the tracheotomy tube and the evacuation of very large quantities of tenacious mucoid material (Fig. 4). The patient was treated with tracheal suction, oxygen, and intravenous iodides, but his condition deteriorated rapidly and he died on his third postoperative day.

Pathology.—The portion of the right cervical lobe of the thyroid gland weighed 75 gm. The intrathoracic thyroid mass weighed 250 gm. (Fig. 5). Both the cervical and the intrathoracic thyroid tumor showed identical histological pictures with involution and colloid changes.

Necropsy revealed marked edema of the larynx. The lower portion of the trachea contained a large quantity of thick fibrinous material which was intimately attached to the wall of the trachea with "finger-like" projections extending into both main stem bronchi. These extensions of fibrinous material were also encountered far peripherally into the finer bronchial ramifications. Examination of the mediastinum showed no appreciable pressure upon the main stem bronchi or trachea by the oxidized Cellulose gauze, and there was a minimal accumulation of old blood.

The final pathological diagnoses were acute fibrinopurulent tracheobronchitis with pulmonary edema, congestion, and partial pulmonary atelectasis; severe edema of the glottis; nontoxic, nodular, cystic, colloid goiter removed at operation.

Valuable time during the operation could undoubtedly have been conserved if the patient had been operated upon while in one position and without the need of redraping. The control of hemorrhage from the numerous venous channels and probably some of the venous radicles arising from the larger veins in the thoracic inlet, such as the innominate, was unsatisfactory through the thoracic approach alone. Despite tracheotomy and bronchoscopic aspirations the patient,

Fig. 5 (Case 1).—Specimen removed from neck and chest.

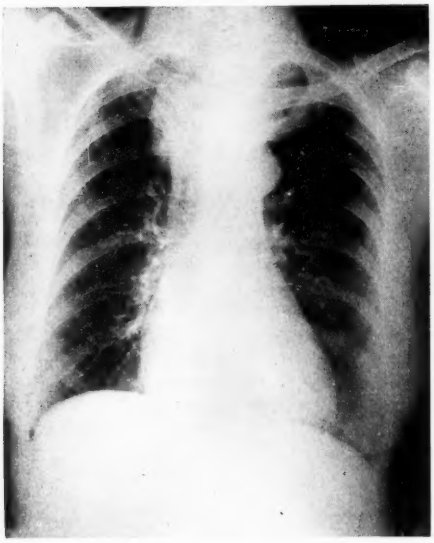


Fig. 6 (Case 2).—P. A. roentgenogram of chest shows large goiter right upper chest.

unfortunately, died as a result of a progressive fibrinopurulent tracheobronchitis, which eventually resulted in obstruction of the smaller bronchial ramifications and asphyxia.

Fig. 7 (Case 2).—P. A. roentgenogram of chest with barium in esophagus shows trachea and esophagus displaced to same side as tumor.

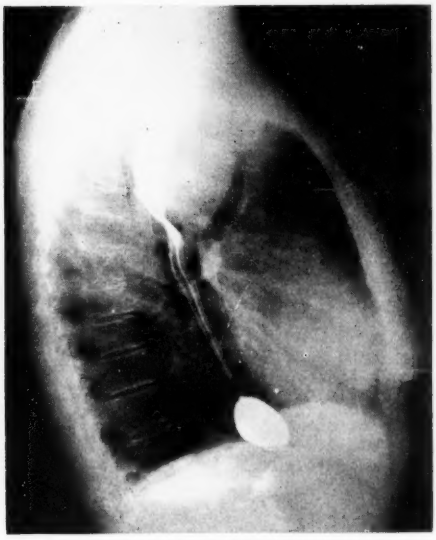


Fig. 8 (Case 2).—Lateral roentgenogram of chest shows goiter descending between trachea in front and esophagus in back with compression and angulation of trachea.

Case 2.—A 58-year-old white woman was admitted to the hospital on Dec. 7, 1952, with a three and one-half month history of dyspnea, wheezing, anterior right chest pain, and constantly recurring upper respiratory infections. The patient

Fig. 9 (Case 2).—Drawing illustrating position of goiter mass behind trachea and great vessels and anterior to esophagus.

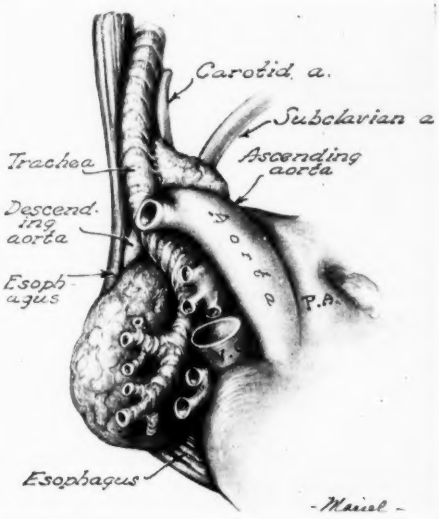


Fig. 10 (Case 2).—Drawing illustrating bi-manual cervicothoracic delivery of retrotracheal goiter from right chest into left neck.

had an intractable hacking cough that was unproductive of blood or pus.

General physical examination revealed no unusual findings. No abnormal enlargements of the thyroid gland were palpable in the neck. The blood pressure was 156/88. The B. M. R. was +18%. The EKG was normal.

Roentgenograms and fluoroscopic examination of the chest revealed a soft tissue mass 10 to 12 cm. in diameter situated in the right upper chest protruding into the right hemithorax (Fig. 6). The trachea and esophagus again were deviated to the same side as the mediastinal mass (Fig. 7). Lateral projection roentgenograms showed anterior displacement and compression of the trachea and posterior dislocation of the esophagus (Fig. 8). On the basis of these findings a diagnosis of large goiter arising from the inferior pole of the left

Fig. 12 (Case 2).—Roentgenogram of the chest 11 weeks after surgery shows normal findings except for persistence of minor shift of trachea to right.

Fig. 11 (Case 2).—Photograph cervical and thoracic incisions at time of discharge from hospital.

lobe of the thyroid gland with extension posterior to the trachea across the midline into the opposite chest was made (Fig. 9).

Operation was performed on Dec. 10, 1952, with the patient under endotracheal anesthesia, supine on the table. Because of previous experiences with a large goiter situated in the same area, it was my intention to utilize a combined cervical and thoracic approach and make a particular attempt to deliver the thyroid into the neck. Accordingly, the usual collar incision was made. No abnormalities were noted in either lobe of the thyroid gland. However, arising in the left infraclavicular region was a large solid goiter which passed behind the trachea and then disappeared deep into the chest. The superior pole vessels were large and elongated and could be seen extending directly into the large thyroid tumor. The vessels were doubly ligated and divided. It was obvious again that it would be impossible to deliver the goiter through this approach alone, and, accordingly, an incision was made in the third intercostal space on the right anteriorly into the pleural cavity. After the insertion of a rib spreader it was obvious that the goiter extended deep into the right chest and protruded beneath the superior vena cava and trachea. With the left hand in the right chest, pressure was made from below while traction was applied with the right hand to the vascular attachments in the neck (Fig. 10). This resulted in surprisingly easy delivery of a large intrathoracic goiter from the right chest, passing behind the trachea and vena cava up into the neck. Some difficulty was experienced when the greatest width of the goiter passed through the thoracic inlet, but additional pressure from below resulted in immediate delivery. It was not necessary to open the mediastinal pleura as it was redundant and permitted passage of the left hand completely across the midline and up into the cervical incision. As soon as the goiter was delivered into the neck, large extremely long veins were identified, easily ligated, and divided. There was very little if any bleeding from the mediastinal pocket. After reexpansion of the lung the thoracotomy incision was closed. A 1-in. gauze pack was placed through the cervical incision into the mediastinal pocket and brought out through the central portion of the wound.

Postoperatively, the patient did exceedingly well. The mediastinal packing was gradually shortened so that it was completely removed by the fifth postoperative day. The patient was ambulatory, afebrile, and ready for discharge from the hospital on her 11th postoperative day (Fig. 11). Roentgenogram of the chest 11 weeks after surgery showed normal findings except for slight shift of the trachea to the right (Fig. 12).

Pathology.—The intrathoracic goiter measured 10.5 by 8 by 5 cm. and showed on microscopic examination extensive nodular involution, hemorrhage and no evidence of neoplastic change (Fig. 13).

The utilization of manual assistance with a hand in one thorax certainly facilitated the delivery of a large goiter mass from an inaccessible position behind the trachea and great vessels and permitted constant control of the major blood supply.

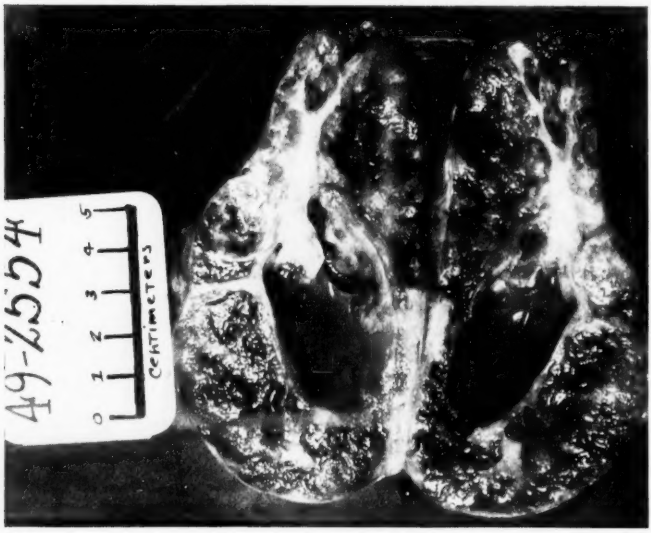


Fig. 13 (Case 2).—Photograph of large intrathoracic goiter showing extensive areas of hemorrhage and involution.

COMMENT

Almost invariably one can suspect preoperatively that a superior mediastinal or intrathoracic tumor is thyroid in origin if it is contiguous with or produces displacement of the trachea on x-ray films of the chest. In doubtful cases the accurate diagnosis may be facilitated by the administration of radioactive iodine followed by uptake determinations with a Geiger counter passed over the region of the tumor.† These determinations were not carried out in the cases reported.

As near as can be determined, protrusion of a goiter between the trachea and esophagus across the mediastinum into the contralateral thorax is an exceedingly rare arrangement, and successful removal of such an abnormally placed goiter has not been reported in the literature. An important finding that should always suggest the correct diagnosis is the displacement of the trachea to the same side as the intrathoracic tumor. Lateral projection roentgenograms will help confirm the retrotracheal position of the goiter.

On the basis of limited experience it would seem preferable to control vascular oozing in the mediastinal space left after the removal of the retrotracheal goiter by packing from above. Opening of the mediastinal pleura to permit drainage into the chest would not offer the beneficial effects of tamponade by gauze from above and might allow continuous bleeding into the chest with a complicating hemothorax. Redundancy of the mediastinal pleura permits easy passage of the hand behind the trachea and vena cava, obviating the need for wide incision of this covering.

Transthoracic manual assistance for delivery of an intrathoracic goiter into the neck was first suggested by Hart,‡ in his discussion of a paper by Adams on "Transthoracic Thyroidectomy," presented before the American Association for Thoracic Surgery in March, 1949.

The thyroid removed by Dr. Hart was located behind the great vessels but apparently in front of the trachea. Biebel,[7] in 1953, one year after the operation recorded in this report, described the technique for removal of a pretracheal substernal goiter whereby the thoracic portion of the mass was supported by a hand in the chest while the interior of the goiter was shelled out by a finger working through a cervical incision above. Then the goiter was delivered into the neck. In most instances reduction of the size of a goiter mass by morcellation would not appear to be necessary, since the viscera in the inlet are compressible and momentary firm pressure from below should accomplish easy delivery of even the largest tumors.

Utilization of a combined cervicothoracic incision with manual assistance through a hemithorax should be of help in any instance of plunging goiter which presents to either side of the midline, but the technique has particular application in those instances where the goiter crosses the mediastinum behind the great vessels or trachea.

SUMMARY AND CONCLUSIONS

As near as can be determined, successful removal of an intrathoracic goiter arising from a unilateral cervical lobe with extension behind the trachea, vena cava, and great vessels into the opposite thorax has not been previously recorded in the medical literature. This arrangement is exceedingly rare and presents unusual problems in surgical exposure, delivery of tumor, and control of blood supply.

Experiences with two retrotracheal goiters and the management of one by a simple bimanual combined cervicothoracic approach without interruption of the continuity of the bony structures about the inlet are reported.

† Touroff, A. S. W., in discussion of Adams.[6]

‡ Hart, D., in discussion of Adams.[6]

REFERENCES

1. Lahey, F. H.: Intrathoracic Goiter, Lahey Clin. Bull. **1**:2, 1939.

2. Dorsey, J. M., and McKinnon, A.: Surgical Management of Intrathoracic Goiter Through the Sternum-Splitting Approach, A. M. A. Arch. Surg. **65**:570, 1952.

3. Rasquin, P.: Tumeur thyroidienne intratrachéale, Ann. oto-laryng. **67**:493, 1950.

4. Lechner, H.: Über das Vorkommen von aortalen, perikardialen und intrakardialen Nebenschilddrüsen, Zentralbl. allg. Path. **86**:383, 1950.

5. McGavack, T. H.: The Thyroid, St. Louis, C. V. Mosby Company, 1951, pp. 298-308.

6. Adams, H. D.: Transthoracic Thyroidectomy, J. Thoracic Surg. **19**:741, 1950.

7. Biebel, M.: Die cervicale Entfernung intrathorakaler Strumen unter manueller Hilfeleistung von einer Brustraumseite aus, Arch. klin. Chir. **276**:402, 1953.

Discussion of Papers by Drs. Ehrenhaft and Buckwalter and Maurer

Dr. John Spencer Harter, Louisville: I certainly agree with what has been said. I want to make one point: ectopic thyroids do appear.

We had a case a couple of years ago who had had a thyroid removed in the usual manner. There was a substernal thyroid which was taken out without any difficulty. Afterward x-rays showed a 5 cm. mass opposite the knob of the aorta. That was explored through the right chest and was found to be an adenoma of the thyroid. The blood supply was easily traced down. The arterial supply came from the arch of the aorta, the venous supply into the superior mediastinum.

I believe this was entirely an ectopic thyroid. The capsule was complete and was easily dissected out. I do not believe it had any relation to the cervical thyroid.

Dr. Warren Cole: I shall confine my remarks to a discussion of Dr. Ehrenhaft and Dr. Buckwalter's paper, since I have been invited to discuss their presentation.

It seems to me that their experience with 13 cases is a relatively large one, certainly much larger than ours; perhaps this is another example of the discrepancies in the incidence of various thyroid lesions. I think they are to be commended indeed for diagnosing 10 of the cases preoperatively, particularly since radioactive iodine is not always diagnostic.

It is also very significant that such a large number of these patients really had significant symptoms, such as cough and dyspnea, which of course tells us something about the anatomical location of the mass. I presume also the anatomical location would explain the relatively low incidence of recurrent nerve paralysis, and perhaps we should expect that.

I believe only three of their cases were thyrotoxic, which is a fortunate circumstance. It conforms to my experience with what I have seen. Only one of ours was toxic, but that case I shall never forget. The patient came to us about 14 years ago, with severe thyrotoxicity of the exophthalmic type. She had very little enlargement of the thyroid lobes, but I fell into the trap of thinking this was one of those cases of hyperthyroidism with mild or no enlargement of the thyroid. We did a subtotal thyroidectomy but she did not have recovery from her hyperthyroidism; this was before the days of thiouracil. She finally died, primarily from hyperthyroidism. At autopsy we found in the mediastinum a nodule 3 or 4 cm. in diameter, which was a hyperplastic thyroid and obviously was the cause of all of her hyperthyroid symptoms.

You will recall that considerable discussion has already been brought out regarding the indication for incision through the neck or incision through the thorax. Dr. Buckwalter has been a little wary about doing some of these through the neck. I agree with that. Of course, if the thyroid is an extention from a lobe in the neck down under the clavicle or sternum, it is easily removed from the neck side, but if there is a complete gap between the normal thyroid and the mediastinal thyroid with no visible vessels leading down to the mediastinal goiter, an attempt to remove it from a neck incision, I am sure, is going to lead to a lot of trouble (primarily hemorrhage) in a large number of those cases. One of our staff removed an upper mediastinal goiter which was completely separated from the neck thyroid in a patient several years ago and had vicious bleeding which he had difficulty in controlling. The patient also bled postoperatively. We finally saved her life, but I think everybody who has tried to attack these cases from the neck has had a similar experience. Some of them bleed badly and require packing, and you worry lest a thoracotomy incision will be necessary to stop the bleeding.

It seems to me that Dr. Buckwalter's and Dr. Ehrenhaft's indications for the type of incision are quite good. For example, you will recall that they advised a sternal-splitting incision for a mass in the anterior mediastinum and a right thoracotomy for masses in the posterior or mid-mediastinum. Since thoracotomy these days is such an innocuous procedure, it seems to me those incisions for goiters located in the areas specified offer a safer approach, where you can really see the vessels and prevent hemorrhage, which sometimes is extremely serious.

Dr. William Holden, Cleveland: Dr. Maurer has very nicely demonstrated a technical maneuver that should be useful on occasion to the general surgeon and the thoracic surgeon, both of whom are occasionally confronted with the problem of removing an intrathoracic goiter. The most serious problem in this situation is the control of the blood supply which, as is well known, most frequently arises from the thyroid vessels themselves in the neck. It is also the common experience of general surgeons that most intrathoracic goiters are mediastinal extensions of cervical goiters and can readily

be delivered through the thoracic inlet after control of the blood supply has been effected through a cervical incision.

Occasionally a large intrathoracic goiter that has extended from the cervical portion of the gland cannot be readily delivered into the neck by means of traction and in these circumstances either splitting the sternum or Dr. Maurer's combined cervical and thoracic approach in most instances should permit delivery of the intrathoracic portion of the thyroid with facility. A rarer type of intrathoracic goiter, arising from ectopic thyroid tissue, has no connection whatsoever with the cervical gland and derives its blood supply from mediastinal vessels. This type of tumor can most satisfactorily be removed through a large thoracotomy.

It is ordinarily an impossible situation to control satisfactorily the blood supply of an intrathoracic goiter through a thoracotomy when its blood supply is derived from the thyroid vessels in the neck. It is also impossible on many occasions to determine whether one is dealing with a cervical extension into the mediastinum or an ectopic mediastinal goiter, and for this reason I feel that a cervical incision should practically always be made initially, since the number of times when this incision alone will permit the complete removal of the goiter is so great. If after the cervical exploration the surgeon finds that he is dealing with one of the ectopic goiters, then an extensive mediastinal exploration through a thoracotomy can either simultaneously or subsequently be performed.

Dr. F. G. Kergin, Toronto, Canada: Dr. Buckwalter made one remark which intrigued me. He said that after one of their operations for an intrathoracic goiter, the patient developed hyperthyroidism.

We have adopted very much the same approach as he has. We have had one patient who had very definitely an ectopic goiter in the chest, with no vascular or other connection with the neck. She was a very thin woman, and her thyroid in the neck was certainly not enlarged. She had no hyperthyroidism.

A large cystic goiter was removed from the mediastinum, and after a period of three or four months she went on to develop a large goiter in the neck. She became hyperthyroid.

Since we believe the activity of the thyroid gland is under hormonal control from the pituitary gland, it seems to be difficult to understand how thyroid tissue in one part of the body could undergo certain changes that lead to cystic degeneration, while the rest of her thyroid gland in the neck was apparently functioning normally until we disturbed the situation by removing a goiter from the chest, and then she went on to develop a large goiter in the neck with hyperthyroidism. I would like to have Dr. Buckwalter comment on his case that developed hyperthyroidism.

Dr. J. A. Buckwalter, Iowa City: I would like to thank Dr. Cole, Dr. Holden, Dr. Harter, and Dr. Kergin for their stimulating discussion.

First of all, one of the three patients who had very mild thyrotoxicosis preoperatively had been operated upon one or two times before for thyrotoxicosis. She had been toxic previously and had been treated for that by conventional subtotal thyroidectomy. There was no question that the thyrotoxic picture developed during the postoperative period. It was necessary to control this with propylthiouracil. Subsequently her thyrotoxicosis went into remission. It also seems of interest that no abnormalities or masses were palpable in her neck at that time.

We hoped to make it clear that the cases we have been interested in are those in which we believed very distinctly we were not dealing with a retrosternal extension of the cervical gland. This other type of case is extremely frequent in our experience, as it is elsewhere, as compared with the true intrathoracic goiter. In approximately half of our patients it would have been physically impossible to remove the gland through the thoracic inlet.

In the one case in which we showed no attachment of the intrathoracic goiter to the cervical gland, a careful search was made and there was no connection in so far as could be determined. This was, in fact, an ectopic thyroid mass within the mediastinum.

Dr. Elmer R. Maurer, Cincinnati: I want to thank Dr. Holden for his comments. I would point out that I have had the same experience as Dr. Harter in patients who have had previous cervical approaches for conventional type goiters, and who have come back with an ectopic intrathoracic goiter. This emphasizes the importance of routine preoperative x-rays of the chest in all persons who have cervical goiters.

I think the surgeon who approaches a thyroid mass near the thoracic inlet should be prepared for a combination of approaches or a single approach, depending upon what he finds at the initial incision. Sometimes there are encountered vessels that go between the trachea or between the innominate vein and thyroid mass, all of which can be determined only at the time of the thoracotomy incision.

I would like to point out briefly something I did not have time to discuss in the presentation of the paper, namely, that the important feature of a combined incision is that the continuity of the thoracic inlet remains intact. It certainly shortens dramatically the operative time, and reduces the amount of blood loss that might be incident to a mediastinotomy incision.

Thyroid Cancer in a General Hospital

DANIEL T. CLOUD, M.D., Phoenix, Ariz.
and
CHARLES D. BRANCH, M.D., Peoria, Ill.

During the last decade there have been a number of reports dealing with the occurrence of cancer of the thyroid. These articles have placed particular emphasis upon the incidence of cancer in the nontoxic solitary thyroid tumor. Ward [1] in 1947 reported a 15.6% incidence in nontoxic solitary nodular goiter. Cole [2] in 1949 reported an incidence of 24.4%, and Crile [3] in the same year found an incidence of 24.5% in this type of goiter. Previous to this time the nodular goiter had been classified as toxic or nontoxic, and the importance of the solitary type of nontoxic nodular goiter had not been emphasized. This high incidence (24.5%) of cancer is in great contrast to the findings of Watt,[4] who in 1951 reported an incidence of 2.5% of cancer in nontoxic solitary nodular goiters from an Atlantic seaboard area.

Sokal * in three recent articles has presented a statistical analysis of malignancy in nodular goiter, attempting to eliminate the factors of screening and selection of cases of which he has been critical. He has concluded that the incidence of cancer is actually higher in toxic than in nontoxic goiter and that there is no evidence in the existing literature to warrant special fear of malignancy in the solitary nodular goiter. His conclusions are in distinct contrast to current surgical opinion. Furthermore, he does not state whether he believes the present accepted indications for surgery of nodular goiter should be changed.

The purpose of this paper is to report the incidence of cancer in a series of goiters removed in a private general hospital serving an urban area, to demonstrate certain differences in the findings as compared with those previously reported, and to discuss possible reasons for these differences. No attempt will be made to discuss diagnosis or treatment of thyroid cancer.

MATERIAL AND METHODS

A review was made of the clinical records and surgical pathology of all patients upon whom a thyroidectomy was performed from 1933 to 1954 in the St. Francis Hospital, Peoria, Ill. Peoria is a farming and industrial community located in the goiter belt. With its surburban area, it has a current population of approximately 250,000. St. Francis Hospital is a private general hospital, and the surgery in the cases reported was performed by 25 different surgeons.

STATISTICAL ANALYSIS

Incidence in each case was computed † as a per cent of the total cases in that category. The statistical significance of the difference between corresponding results as reported by different authors was checked by use of the standard error of the difference between means. Although the original distributions of the respective incidences were of the Poisson type, the sampling distributions of their differences were approximately normal. A standard error as large as three, therefore, indicated a significant difference.

Submitted for publication April 25, 1955.

From the Department of Surgery, St. Francis Hospital, Peoria, Ill.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

* References 5, 6, and 7.

† Dr. Lucile Derrick, College of Commerce, University of Illinois, performed the statistical analysis.

TABLE 1.—*Type of Goiters Occurring in this Series*

	No. of Cases
Total goiters	814
Toxic goiters	420
Nodular	234
Multinodular	177
Solitary nodular	57
Diffuse	186
Nontoxic goiters	394
Nodular	291
Multinodular	174
Solitary nodular	117
Diffuse	103

RESULTS OF STUDY

In arriving at the clinical and anatomic classification of the material studied, all available evidence in each case was reviewed. It immediately became apparent that the recorded peroperative clinical impressions as to whether the goiters were solitary nodular or multinodular would be of no value in this series because of variations in terminology. Also, because of the emphasis we intended to put on cancer occurring in nodular goiter, no gland was classified as solitary nodular or multinodular unless an absolute positive finding to that effect was demonstrated in the material at hand. Those without positive evidence were arbitrarily placed in the diffuse goiter class. It may therefore be that the number of diffuse goiters reported, particularly nontoxic diffuse goiters, is erroneously high.

In this series there were a total of 814 goiters which had been removed at the time of thyroidectomy. Of these, 420 were toxic goiters and 394 nontoxic goiters. In the group of 420 toxic goiters, 234 were nodular goiters, 177 showing evidence of more than one nodule, and 57 having a single nodule. In the group of 394 nontoxic goiters, there were 291 nodular goiters, of which 174 were multinodular and 117 solitary nodular goiters. The average age of the entire group was 43.2 years. The percentage of Negroes was 4.2%. Of the nodular goiters 86.4% were in females and 13.6% in males.

All cancers were found in the group of nontoxic goiters. There were a total of 22 cases, 9 occurring in multinodular goiters, 8 in solitary nodular goiters, and 5 in diffuse goiters. The incidence of cancer in the entire series of 814 goiters was 2.7%. In all nontoxic nodular goiters the cancer incidence was 5.8%. A breakdown of that group showed a cancer incidence of 5.2% in multinodular goiters and 6.9% in solitary nodular goiters. It is important that these latter figures do not differ significantly. An incidence of cancer of 4.8% was found in the nontoxic diffuse goiters. The sex distribution showed that, of the 22 cases of cancer, 19 (86.4%) were in females and 3 (13.6%) in males. The average age of the group of cancer cases was 45.5 years, the extremes being 28 and 85 years.

In testing the significance of the important difference between these figures and those of other observers, a standard error of 3.56 or over was found, with one exception, in every case, indicating that the differences were of such magnitude that factors other than sampling errors must have been responsible for them. The exception was found in testing the difference between our figures and those of Watt, who reported a lower incidence of cancer. In that difference no significance was found. However, a test of the difference between the figures of Watt and Cole or Crile revealed definite significance.

COMMENT

It is immediately apparent that there are some interesting discrepancies between the findings in this series of cases and other

TABLE 2.—*Cases of Cancer of Thyroid and Incidence of Cancer*

		No. of Cases
Cancer of thyroid in goiters		22
Nontoxic nodular		17
Multinodular		9
Solitary nodular		8
Nontoxic diffuse		5
Incidence		**Per Cent**
In the total series		2.7
All nontoxic nodular goiters		5.8
Multinodular goiters		5.2
Solitary nodular goiters		6.9
Nontoxic diffuse goiters		4.8
Sex distribution		
Females	19	86.4
Males	3	13.6

series that have been reported, especially with regard to the incidence of cancer in nontoxic solitary nodular goiters. Watt reported a lower incidence of cancer (2.5%) in that group, but, as stated above, no significant difference exists between this figure and ours.

The 24.5% incidence of cancer in nontoxic solitary nodular goiters reported by Crile is, of course, much higher than that found in this series, and it may be explained at least partially by the fact that Crile does not advocate removal of asymptomatic nodular goiters unless their palpable consistency suggests malignancy. The similar high cancer incidence reported by Cole and his associates is based on a series in which routine removal of all solitary thyroid nodules is advised. Thus there has been no screening of the patients to account for the differences in incidence between this series and ours.

A study of 22 cancer cases in this series indicates another discrepancy as compared to a previous report. The incidence of males with cancer was found to be 13.6%, a figure comparable to a 12.8% incidence of males in the entire nodular goiter group and identical to the incidence of males (13.6%) in the nontoxic nodular goiter group. Cole reported an incidence of 10% males in the total nodular goiters and an incidence of 33.3% males in the group of cancers. From this he concluded that the probability of development of cancer in nontoxic nodular goiters is three times greater in men than in women. It is obvious that our findings do not warrant such a conclusion, and an analytical comparison bears this out. In addition, Ward reported the incidence of cancer in men with nodular goiter in his entire series to be 12%, with a rise to 16.6% in the more recent years. Cole found a similar incidence of 17.5%. He also noted a recent increase in the incidence. In our series of cases, however, we found the incidence of cancer in men with nontoxic nodular goiter to be only 5%. The fact that we found no case of cancer in a toxic goiter is not significant inasmuch as such a lesion has been found only rarely by other observers. We found no important difference in age, sex, or race.

It would also seem that too much emphasis has been placed on the solitary nodular goiter without further clarifying just what is a solitary nodule. Although we were unable to determine accurately in this series the likelihood of correctly diagnosing a solitary nodular goiter preoperatively, it has been clearly shown by Beahrs [8] that such a diagnosis is difficult to make correctly. He concluded that a preoperative classification of goiters on the basis of how many nodules are thought to be present has little value. In other words, the fact that only a single nodule is palpated in the goiter preoperatively does not necessarily mean that the surgical pathologist will not find more nodules. One can therefore seriously question the absolute importance of the solitary nodule as a clinical entity. This has been emphasized recently by Martin,[9] who has stated that, while some thyroid cancers do arise in preexisting adenomas, it has been abundantly established that thyroid cancers can arise independently in non-neoplastic thyroid tissue. He further states that in the Memorial Hospital in New York the incidence of cancer is almost twice as high (15%) in multiple tumors of the thyroid as compared to its incidence (8%) in solitary tumors. As indicated previously, in our group of cancer cases no significant differences were found between the various anatomical types.

However, in spite of wide variations in figures in the numerous reports on cancer of the thyroid, the danger of cancer occurring in nontoxic nodular goiter is certainly a real one. It seems likely that the real probability of occurrence will not be determined until a sufficient number of cases are reported to enable one to eliminate all of the various factors that have been said to account for present differences. Certainly the indications for thyroidectomy in nontoxic nodular goiter are unchanged, but perhaps one should not consider the patient presenting what is thought to be a solitary nodule to have one chance in four of the lesion being malignant.

SUMMARY

Cancer is a factor to be considered in the treatment of nontoxic nodular goiter. A review of 814 consecutive thyroidectomies done in a general hospital shows an incidence of cancer of 5.8% in all nontoxic nodular goiters, with no significant difference in incidence between the multinodular and solitary nodular groups.

DISCUSSION

DR. EDWARD S. JUDD, JR., Rochester, Minn.: We do not wish to belabor the issue in regard to nodular goiter and carcinoma; however, we do have to take a stand and be prepared to defend our stand.

We are called on to consult upon a large number of patients who may have a goiter as a purely incidental finding and who are examined for an entirely different reason. In discussing the possibilities with the patient, we should like to be prepared to have some idea of what the possibilities are.

About the only thing we have done in the past that may be erroneous thinking is to analyze our surgical figures every year, that is, to simply take the number of goiters and find out how many were malignant. We have come up with a surprisingly standard figure each year.

We say that about 5% of the multiple nodular goiters are malignant, and that seems to prove true. For some peculiar reason about twice that number (around 10%) of the single or discrete ones are malignant.

Dr. J. D. Mortenson, one of our surgical residents, has recently completed a tremendous survey of 1000 consecutive autopsies in which he personally did serial sections on the entire thyroid gland.

[Slide] I call your attention simply to this one figure, primary carcinomas that he found in these nodular glands.

We think it simply backs up some of the surgical thinking we have done, and we are going to continue to urge prophylactic surgery for these people.

DR. CLAUDE J. HUNT, Kansas City, Mo.: There is much disinterest on the part of the profession at large concerning the problem of nodular goiter, and usually they take no interest in it until the lesion becomes large or mechanical factors related to the increasing nodular size become evident.

They do not consider the potentialities of this goiter from the standpoint of malignancy, and I think it is well that we talk about such possibilities in our communities, because the potentialities are really higher than most people think.

In 100 thyroidectomies for nodular goiter we had 11 cancers; the age limit was from 17 to 73. Nine of the patients were below the age of 29, demonstrating the fact that nodular goiter in a young person is more likely to be malignant than those old degenerative goiters that occur in older people.

This past year, in addition to this series of 100 cases, we had 4 malignant goiters, and the youngest patient was 11 years old. That little boy had been taken to several doctors because he had a nodule in his neck. It was pronounced innocent or it was attributed to some other cause, adenopathy. The boy had very extensive thyroid carcinoma when he came to us, with a glandular metastasis on each side of the neck.

We did a bilateral radical neck dissection. He has since returned with a palpable node in the right posterior triangle of the neck, and we did a radioiodine uptake study on him. At only one location was there a response. This was in the posterior triangle. We removed several glands, one of which was malignant.

In another instance a 23-year-old woman, with a family, was seen recently with a nodular goiter and associated glandular invasion on the left side. For three years she had had a nodular goiter. On several occasions she had consulted varous physicians about having something done. She was told it was simply an old nodular goiter; it was not harmful. We did a radical neck dissection along with total thyroidectomy. All nodes were involved. This presents again the disinterest that is prevalent about nodular goiter.

The incidence of carcinoma of the thyroid in nodular goiter is certainly something we must keep in mind at all times. We have had a little over 10%. Dr. Cole and others have reported a very high percentage. As reported here today, it is much lower, but at any rate it is sufficiently high so that all people with nodular goiter, whether it is supposed to be a discrete nodular goiter or a multiple nodular goiter, should have the nodules removed.

Whatever the incidence is—4, 5, 8 or 24%—the incidence is so much higher than the mortality rate for removing them that they should all be removed. The mortality rate for nontoxic nodular goiter should be, in fact, nil.

DR. WARREN COLE, Chicago: This paper is very intriguing to me because it illustrates another example of inconsistencies in the incidence of thyroid lesions, and it emphasizes still more the fact that we are poorly informed on the pathogenesis of goiter, including thyroid cancer. I am quite sure that the pathogenesis of goiter itself is related to the pathogenesis of the cancer, but I have no idea in what way.

You will recall the authors' incidence of 5.8% cancer in nontoxic goiter. That is less than half of that which we have reported from Chicago and which Crile and others have reported. In fact, the highest incidence of all is in New Orleans. They now have the record for the highest incidence of cancer in nodular nontoxic goiter.

What is the explanation for this tremendous difference in incidence? I am convinced now that it is not a difference in the diagnostic critera. I believe that all pathologists now understand well enough the variations of toxic goiter so they will not make many mistakes. Of course they will make a few, but they will not make mistakes running up to 200 or 300%.

I am quite convinced that the geographical location exerts a strong influence on this disease. It seems to me that this supposition is supported very strongly by the fact that some clinics have such a low incidence and yet have a very high five-year survival.

For example, take the Mayo Clinic statistics: Judd and Beahrs reported 3.8% incidence of carcinoma in nontoxic nodular goiter, with 71% five-year survivals, whereas we had 15.6% and only 36% five-year survivals. I think that point right there is enough to tell us that there is something far different in the type of malignant goiter they are seeing at Rochester from what we are seeing in Chicago. If they had a high incidence with the high five-year survival, we might think they were making the diagnosis too liberally, but the opposite is true. So I am driven to the supposition that there must be a geographical difference.

Another point suggesting that the carcinomas may be of a different type is the fact that in their patients with nodular goiter Dr. Cloud and Dr. Branch had the same incidence of cancer in men as in women. In our series, the possibility of carcinoma is three times as great in men as it is in women.

To a certain extent the screening which takes place (automatic or otherwise) is important in the incidence; accordingly, the incidence figures reported do not imply that such a percentage of persons with goiters walking the streets have a cancer; nobody has ever made that claim: It simply means that by the time the patients finally go to a doctor, a certain percentage of them have carcinoma.

I should like to call attention to the difficulty in making the diagnosis, which has been alluded to by some of the other speakers. We were able to make the preoperative diagnosis in 46%; also in 46% the diagnosis was made first in the surgical pathology room, whereas in 8% of patients the diagnosis was made at the operating table. In other words, in our clinics we are not very good at making the diagnosis of carcinoma of the thyroid unless there is massive infiltration.

In going over the signs and symptoms, we noted that the incidence of soft consistency or hard consistency, rapid growth, cough, choking, and pain was the same in the two groups; so we had no help at all from those manifestations. The only difference we found which could help us in diagnosis was the fact that hoarseness was noted in 38% of the patients with carcinoma but in only 21% of the patients with benign nodules. Vocal paralysis, i. e., nerve paralysis, was noted in 0% of 50 cases with nontoxic nodular goiter, and 29% of those having cancer. So actually, the secondary effect on the recurrent nerve is about the only significant manifestation that we can find which helps us in differentiating those two lesions.

DR. J. C. T. ROGERS, Urbana, Ill.: I hesitate to make and comment whatsoever after Dr. Cole's authoritative discusion on this subject; but, since Drs. Cloud and Branch come from down in my area, I should like to make a brief comment about my personal experience with thyroid cancer.

In this very interesting problem, one is justifiably puzzled by the variations in the published data. For some years the internists in my group have questioned the high incidence of carcinoma of the thyroid reported. I am sure that what Dr. Cole has stated—that pathologists are more or less in agreement as to classification and criteria in thyroid disease—is true. However, there still exists that personal equation which in each instance plays a role in determining when a gland ceases to be hyperplastic and when it begins to be anaplastic.

With that in mind, I wish to report 119 personal cases over the last three and one-half years. I have selected the three and one-half-year period because it is the tenure of our present pathologist, who studied the tissues in these cases.

There were five instances of reported carcinoma, an incidence of 4.2%. All occurred in nodular glands and were of the papillary adenocarcinoma type. One showed demonstrable invasive features.

I reluctantly mention this relatively small group of cases. On the other hand, a pooled experience of many of us in the more or less outlying areas and not in the large metropolitan and teaching centers may conceivably contribute valuable information on the subject.

Drs. Cloud and Branch have presented data which suggest variations in thyroid disease dependent upon environmental conditions. It is known that this is a factor which can influence the behavior of other nonexcretory glands.

DR. DANIEL T. CLOUD JR., Chicago: I should like to thank Drs. Judd, Hunt, Cole, and Rogers for discussing our paper so ably.

I believe Dr. Hunt's remarks about the importance of performing surgery for nodular goiter are very well taken. We hoped to emphasize that we did not feel the indications for surgery have changed, in spite of the fact that there are wide variations in the figures reported as to the incidence of cancer.

I also want to thank Dr. Cole for further amplifying many of the reasons and possible reasons for differences in these various reports.

REFERENCES

1. Ward, R.: Malignant Goiter: Lessons to be Learned from a 20-Year Follow-Up, West. J. Surg. **55**:383, 1947.

2. Cole, W. H.; Slaughter, D. P., and Majarakis, J. D.: Carcinoma of Thyroid Gland, Surg., Gynec. & Obst. **89**:349, 1949.

3. Crile, G., Jr., and Dempsey, W. J.: Indications for Removal of Nontoxic Nodular Goiter, J. A. M. A. **139**:1247, 1949.

4. Watt, C. H., and Foushee, J. C.: The Incidence of Carcinoma in Nodular Thyroids in Southwest Georgia, J. M. A. Georgia **40**:414, 1951.

5. Sokal, J. E.: Occurrence of Thyroid Cancer; New England J. Med. **249**:393, 1953.

6. Sokal, J. E.: The Incidence of Malignancy in Toxic and Nontoxic Nodular Goiter, J. A. M. A. **154**:1321, 1954.

7. Sokal, J. E.: Surgical Statistics on Malignant Goiter, Surg., Gynec. & Obst. **99**:108, 1954.

8. Beahrs, O. H.; Pemberton, J. de J., and Black, B. M.: Nodular Goiter and Malignant Lesions of Thyroid Gland, J. Clin. Endocrinol. **11**:1157, 1951.

9. Martin, H.: The Surgery of Thyroid Tumors, Cancer **7**:1063, 1954.

Isotope Techniques for Mediastinal Tumors

ROBERT D. SWEDENBURG, M.D.
WILLIAM M. TUTTLE, M.D.
and
K. E. CORRIGAN, Ph.D., Detroit

Our current diagnostic methods and specialized surgical skills still leave much to be desired in the results obtained by many of us in our present practice of medicine. One phase of this desire falls into the field of mediastinal tumors.

Much has been written regarding the diagnosis and surgical treatment of these tumors. The classical diagnostic techniques of clinical evaluation have been enhanced so greatly by the roentgenologist and modern laboratory facilities that the correct diagnosis can be made in approximately 80% of the cases preoperatively, as stated by Curreri and Gale.[1] In the remaining 20%, namely those with confusing mediastinal shadows, accurate isotope techniques can dispel the confusion and actually guide the surgery. A single tracer study, or at most a sequence of two, will serve to divide all mediastinal tumors into three general groups: (1) thyroid, (2) fast-growing tumors, and (3) the relatively inactive masses, such as cysts and fibromas.

It is not the purpose of this paper to enumerate the accepted work of those * who have categorized the signs, symptoms, x-ray morphology, and topography, as well as statistical probability of chance occurrence of a given tumor and its predilection for a given mediastinal compartment. The last three criteria are presumably the best resources for attaining a correct diagnosis, excluding the direct attack of x-ray therapeutic test dose, biopsy, or exploration, since the tumor can be present so frequently without associated signs or symptoms.

Since January, 1947, radioactive isotopes have been used extensively at Harper Hospital. Iodine (I^{131}) has no doubt established its value as a tracer substance for the thyroid. Accurate clinical and physical interpretations of the localizations of this isotope by the Geiger-Mueller counter have led to more precise understanding of that mediastinal shadow produced by the displacing diseases of the thyroid gland.

Radioactive phosphorus (P^{32}) is likewise used as a standard tracer, if our confusion still exists after the use of radioactive iodine (I^{131}). The radioactive phosphorus is metabolized by all growing structures and in direct ratio to their rate of growth. It is, therefore, concentrated rapidly by the fast-growing malignant lesions and to a lower degree by the slower-growing malignant tumors.[16] The lymphoma group will generally reveal themselves by a high and early concentration of the tracer. The P^{32} tracer in effect serves the purpose of the therapeutic test dose of x-rays, but the results are obtained in a few days, compared with a three to six week response from radiation.

The following is an explanation of the method of tracer approach to the problem of a confusing mediastinal mass. In view of the frequency,[17] unusual positions, and outline that may be assumed by a mediastinal thyroid, including a posterior mediastinal position, radioactive iodine (I^{131}) tracer should be conducted first. By necessity this procedure should, if its use is anticipated, precede any special x-ray techniques requiring the use of radiopaque material, since these substances will delay the effective use of I^{131} for some time. For this same reason the isotope

Received for publication April 25, 1955.
Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

* References 1 to 15.

team is likewise interested in the patient's recent use of any iodine-containing substance.

A standard dose of 50μc of radioactive iodine (I^{131}) in solution is given by mouth at 8 a. m. to the patient in a fasting state. Close contact scanning with the Geiger-Mueller counter is started two hours after the dose is given. This time interval has been found adequate for absorption of the tracer dose, and the data obtained are recorded as the first count. Close contact scanning differs from that of the fixed distance count over the thyroid area. The instrument is maneuvered over the skin surface, beginning in the normal thyroid region and working systemically over the cervical region and progressing caudally over the chest in a symmetrical pattern for the right and left sides. Scanning is also done over the liver, epigastrium, and other organs in a routine manner. All data are recorded in counts per minute and charted with reference to the time the count is taken. In this manner the anatomical framework is surveyed.

The tracer study is repeated at approximately six-hour intervals for a total of not less than three complete counts the first day. The following day a 24- and a 32-hour count are taken and, depending upon the information derived, the study may be extended to 48 or 52 hours. During the tracer procedure each and all of the urinary specimens are collected and the time of passage is recorded. Aliquot portions of these specimens are then assayed for radioactivity, and the per cent obtained per specimen is calculated. From these data an excretion curve is plotted.† If the lesion in question is not of thyroid origin, and this can be tentatively assumed from the early sequential counts, this tracer rapidly clears from the blood stream, making other studies possible.

Radioactive phosphorus (P^{32}) is then administered. A dose of 100μc of P^{32} in solution is given by mouth. Twenty-four hours is allowed for absorption and metabolism of this tracer, since its subsequent localization depends upon its incorporation within the cell structure. Close contact scanning is the method of choice again, and the first count is taken 24 hours after administration of the tracer dose. The data obtained are charted in counts per minute according to the surface topography of the recorded counts, and a second complete count is taken 48 hours later. The bony structures in particular are surveyed to establish a base line count. The important criterion is that a given localization count must be repeatable to be considered valid.[16]

† References 18, 19.

REPORT OF CASES

The following cases are illustrative of the value that may be achieved by accurate isotope technique.

CASE 1.—A 66-year-old white woman was admitted to Harper Hospital Aug. 30, 1948. She had been short of breath for one year, with associated palpitations. After this she became nervous and developed a coarse tremor. Three months before admission a nonproductive cough and a sense of compression about the throat were noticed. She had had a chest x-ray and bronchoscopy in another city two weeks prior to admission and was told she had "a goiter or growth." She had had a right nephrectomy some years previously.

Physical examination revealed an obese white woman appearing very nervous but otherwise in good general condition. There were no abnormal physical findings. X-ray studies (Fig. 1) revealed a mediastinal mass. An I^{131} tracer study, performed on Sept. 1, 1948, was of no value because of a chemical block. It was learned that the patient had been using an iodine cough preparation prior to admission.

The patient was discharged from the hospital and readmitted Sept. 6, 1948. A second tracer study, using a dose of 50μc of I^{131}, was performed on Sept. 7, 1948. The mass (Fig. 2) behind the upper portion of the sternum extending to the third interspace was found to be of thyroid origin. Prior to operation on Sept. 8, 1948, the lesion was outlined on the anterior chest wall. The mass was approached through a sternum-splitting incision, and a large pear-shaped tumor, 9×7×4 cm., weighing 150 gm., was removed (Fig. 3). The normal thyroid region was then explored and a large mass was found on the left measuring 9×3×3 cm. and weighing 52 gm. A small mass, 6×4×2.5 cm., weighing 35 gm., was also removed on the right. Pathologic diagnosis was "thyroid adenoma with cystic degeneration and fibrosis."

CASE 2.—A 22-year-old white woman was admitted to Harper Hospital Jan. 25, 1953, with a

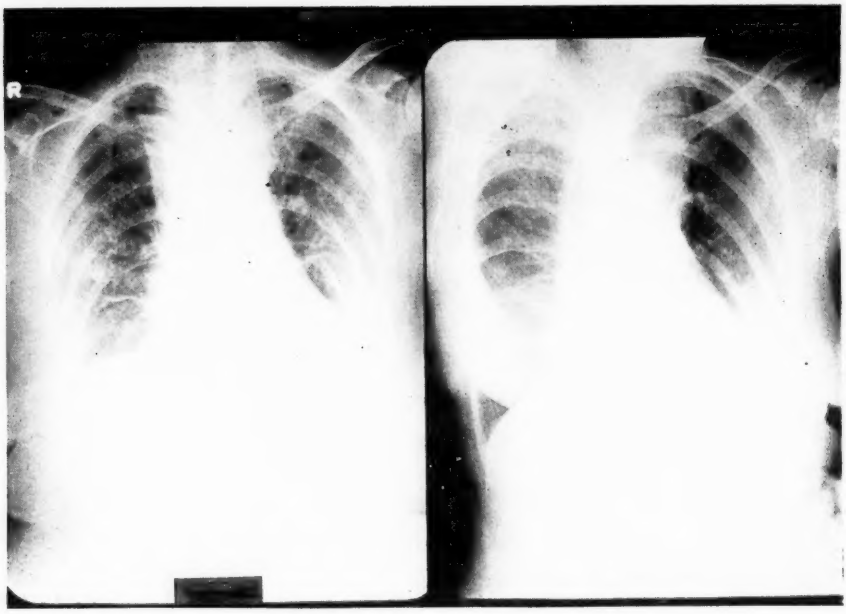


Fig. 1 (Case 1).—X-ray appearance Sept. 1, 1948.

Fig. 2 (Case 1).—Tracer map Sept. 8, 1948.

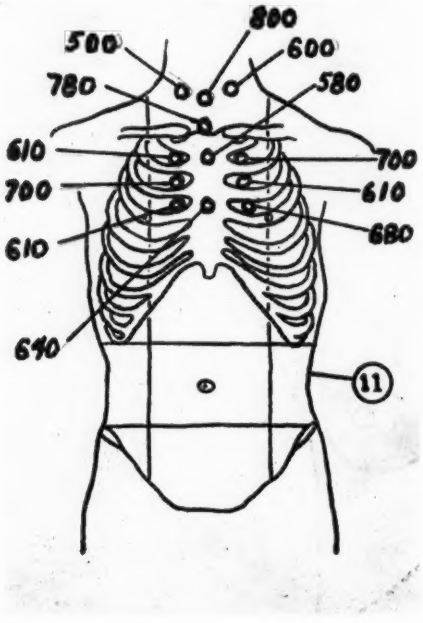
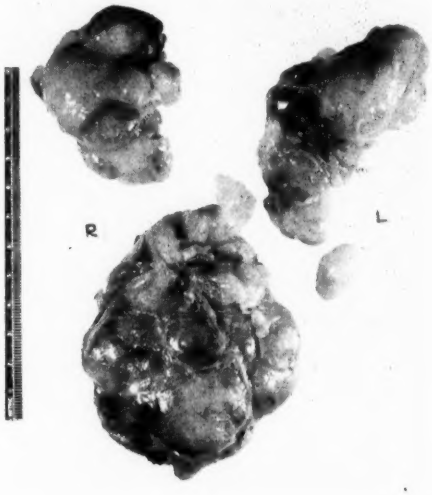


Fig. 3 (Case 1).—Gross specimen of the mediastinal tumor of thyroid origin.



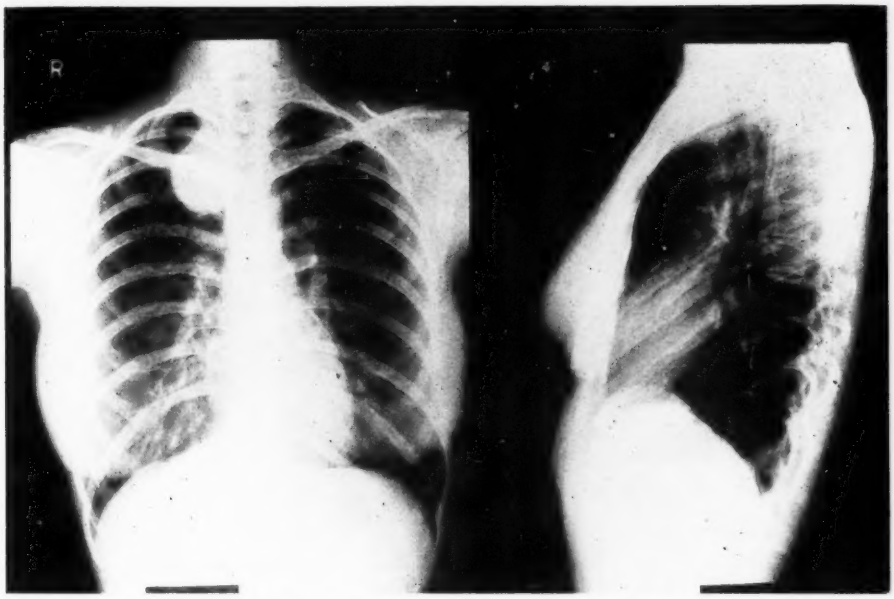


Fig. 4 (Case 2).—X-ray appearance Dec. 31, 1952.

history dating back to 1945, when she had a cancerous growth removed from the anteromesial aspect of the left tibia. The growth recurred and was again removed in December, 1949. The pathology report was osteomyochondrosarcoma. Aug. 28, 1950, was her first admission to Harper Hospital, and x-ray examination at that time had revealed a lesion in the tibia, but both lungs were clear. Local excision of the tumor mass was done on Aug. 31, 1950. On Jan. 9, 1951, the patient was readmitted, and on Jan. 10, the left leg was amputated at the supracondylar level. The pathologic diagnosis was chondrosarcoma, more cellular.

Her present admitting symptom was pain under the right scapula of three months' duration. The x-ray examination (Fig.4) revealed a mass in the region of the right upper lobe posteriorly. Physical examination was essentially negative except for the absence of the left leg, with a well-healed stump. P^{32} tracer studies conducted Jan. 3, 1953, revealed localization of this isotope in the region of the mass seen on x-ray (Fig. 5). The concentration of the isotope was that of an actively functioning mass. A right upper lobectomy was done on Jan. 26, 1953, with hilar node dissection (Fig. 6). The pathologic report revealed chondrosarcoma, lymph nodes not involved. The patient had an uneventful postoperative recovery and was discharged Feb. 3, 1953.

During the next few months her general condition was good, and periodic x-rays were satisfac-

Fig. 5 (Case 2).—Tracer maps showing localization right upper lobe 3 years after first study.

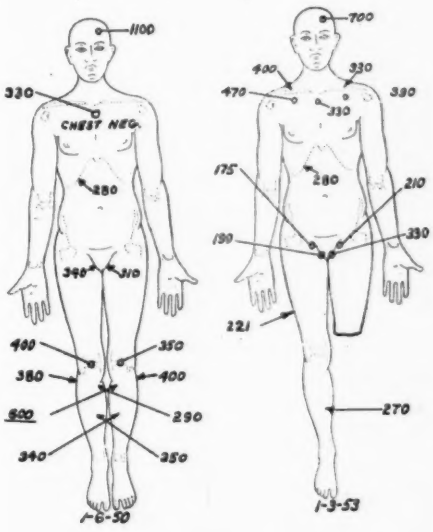
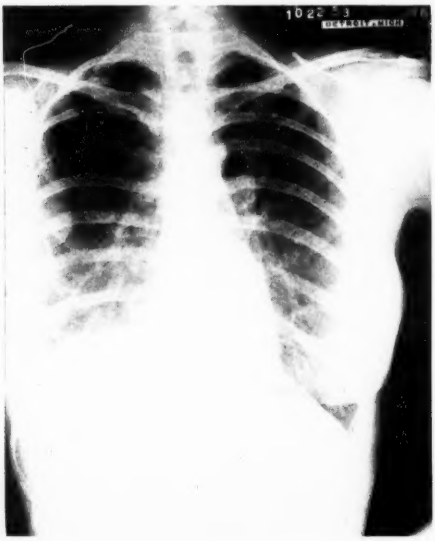


Fig. 6 (Case 2).—Gross pathological specimen.

tory. The patient returned to her physician to inquire whether or not it was all right to become pregnant. An x-ray taken at this time, Oct. 22, 1953, (Fig. 7) showed a homogenous ill-circumscribed mass in the right chest at the level of the sixth and seventh interspace. No other definite lesions could be seen in the right or left lung. On Oct. 26, 1953, a tracer dose of 100μc of P^{32} was administered, and subsequent study with the Geiger counter revealed two major localizations. One was 3 to 5 cm. to the left of T-1, the other was about 5 cm. to the left of T-8 and T-9. A survey over the right hemithorax revealed no definite localizations. In view of the pulmonary metastases, the patient was started on deep x-ray therapy Nov. 16, 1953.

She was again admitted to the hospital, Dec. 2, 1953, because of esophagitis secondary to the deep therapy and was treated symptomatically and discharged Dec. 16, 1953. Her final admission to the hospital, on Feb. 8, 1954, was necessitated by rapid progression of the disease (Fig. 8). Her

Fig. 7 (Case 2).—X-ray appearance Oct. 22, 1953.



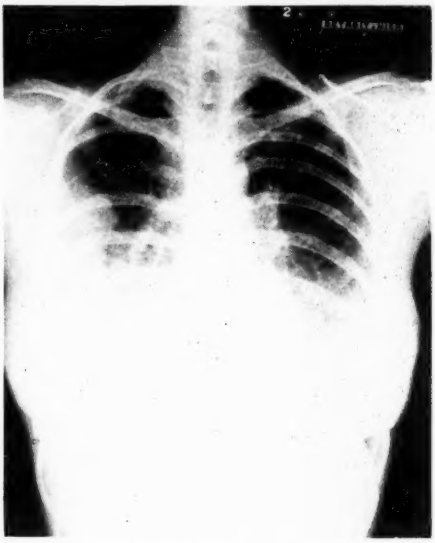


Fig. 8 (Case 2).—X-ray appearance Feb. 8, 1954.

chief complaint on admission was shortness of breath. She died Feb. 23, 1954.

An autopsy was obtained and the findings revealed a lesion 9×5×4 cm. in the lateral portion of the right lung which was a metastatic lesion. Interestingly, the left lung revealed two 1 cm. nodules which were metastatic lesions, one being in the apex and the other at the base of the lung. It seems likely to assume that the localization of the P^{32} was quite accurate for these two lesions in the left lung. The question arises as to whether or not the lesion in the right lung had been present since October and, if so, whether or not the lesion was too minute or screened out by a localized collection of pleural fluid which was found in this region at autopsy.

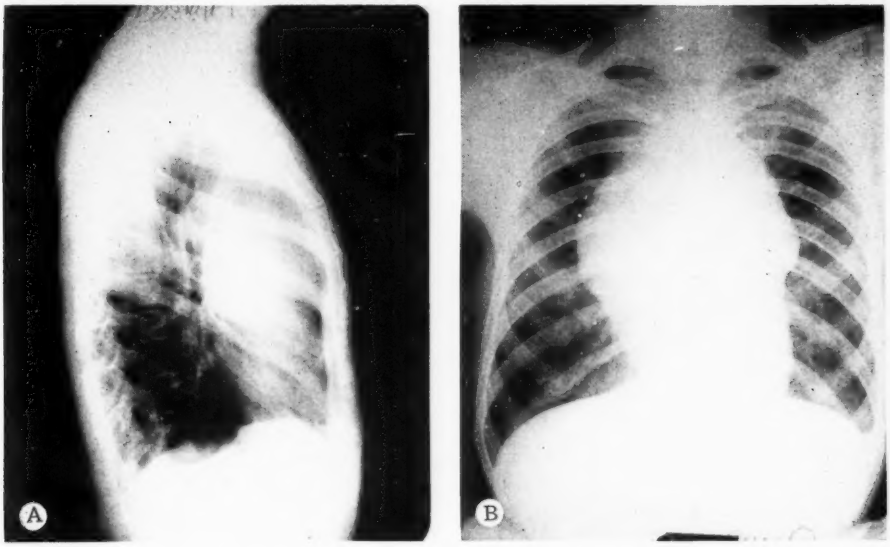
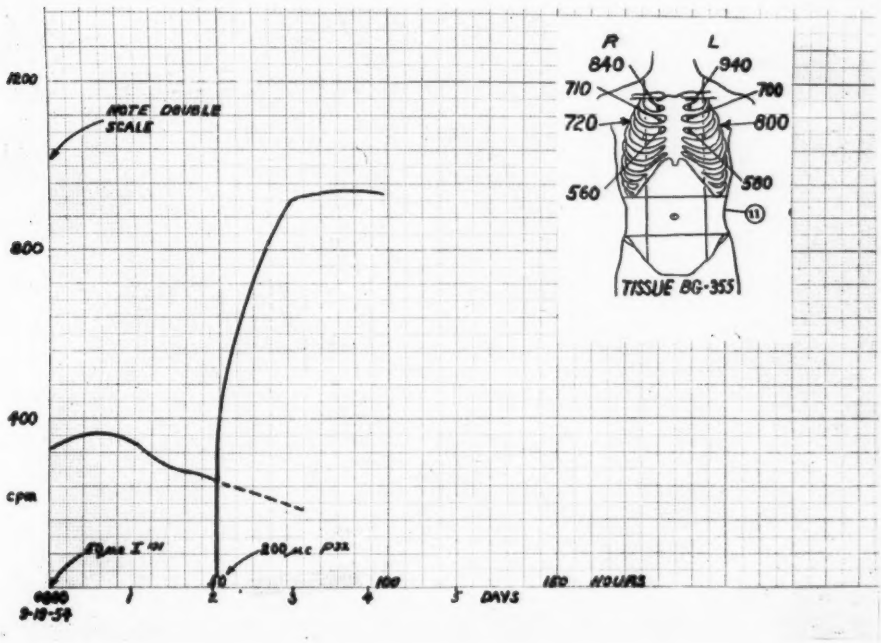


Fig. 9 (Case 3).—X-ray appearance Sept. 1, 1954.

Fig. 10 (Case 3).—Tracer map and concentration curves September, 1954, showing negative result with I^{131} and strongly positive localization with P^{32}.



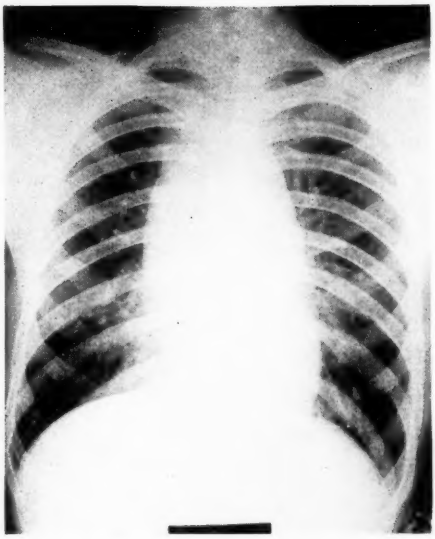


Fig. 11 (Case 3).—Post-therapeutic appearance Jan. 7, 1955.

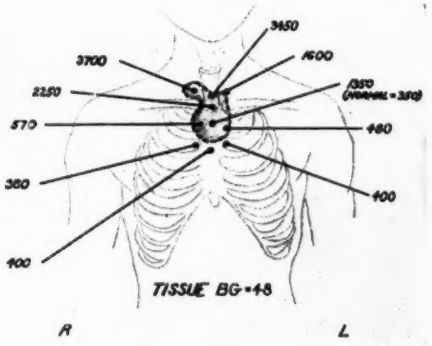
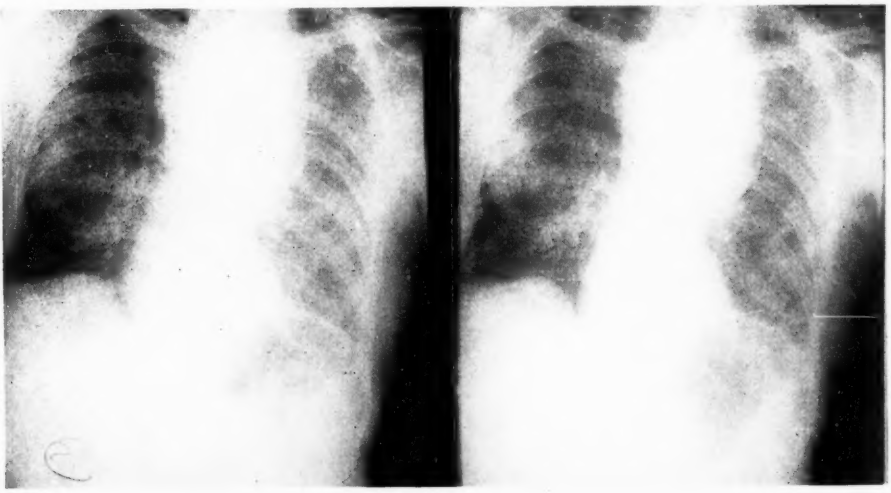


Fig. 13 (Case 4).—Tracer map Oct. 28, 1948.

Case 3.—A 29-year-old white man was admitted to Harper Hospital Sept. 1, 1954. He had been in his usual state of health, and during a pre-employment x-ray examination on Aug. 11, 1954, a mediastinal mass was detected. Previous x-rays, in 1948, had revealed no mediastinal mass. His appetite had been good, although he had lost some weight between April and this hospital admission. In January, 1954, the patient had been treated for a cold. He had been ill for two weeks with fever, left anterior chest pain, and a cough which had persisted to the time of this admission.

Physical examination revealed palpable nodules, 1 cm. in diameter, in each axilla; otherwise the examination was negative. Special blood studies for cell morphology did not appear abnormal. X-ray examination (Fig. 9) revealed a large anterior mediastinal mass. An I^{131} tracer study revealed no significant thyroid abnormality. A P^{32} tracer study demonstrated localization in the known mass and indicated that is was an active but relatively slow-growing type (Fig. 10). Bronchoscopic examination of this patient was essentially negative, and a left axillary node biopsy was reported as chronic lymphadenitis. On Sept. 15, 1954, a mediastinotomy was done and a large mass was found beneath the sternum. A biopsy

Fig. 12 (Case 4).—X-ray appearance Oct. 8, 1948.



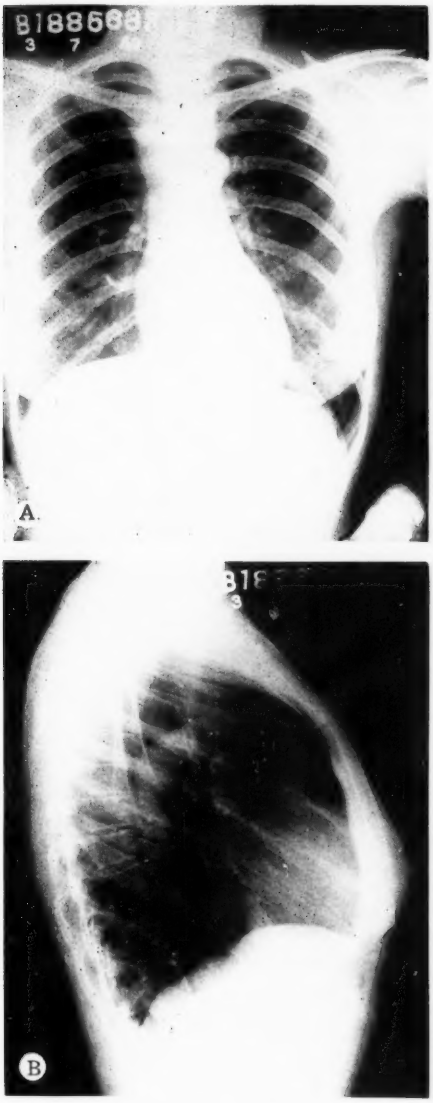


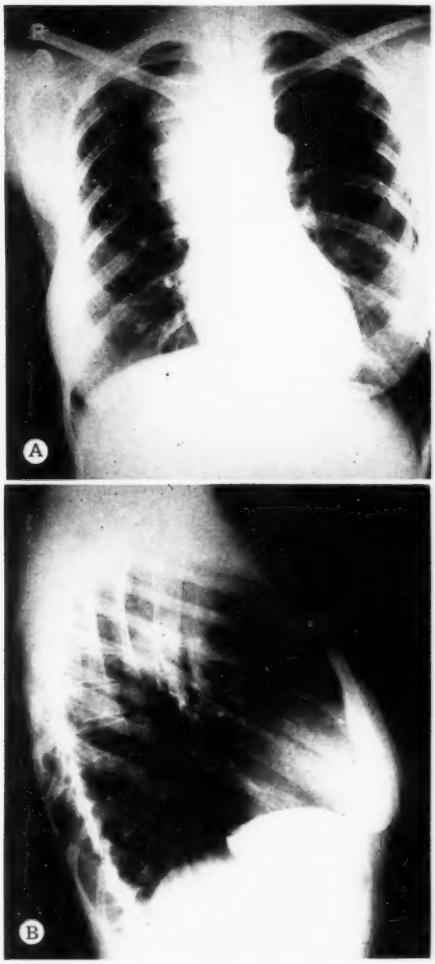
Fig. 14 (Case 5).—X-ray appearance March, 1949.

of this mass on frozen section was reported as indicating malignant changes, and a final pathological diagnosis of Hodgkin's disease was made. Postoperative recovery was uneventful, and subsequently the patient was treated with radiation therapy and nitrogen mustard. He was last seen Jan. 7, 1955 (Fig. 11), when he was asymptomatic and responding to his current treatment.

Case 4.—A 44-year-old Negro man was admitted to Harper Hospital Oct. 8, 1948, for evaluation of cough and voice change of two months' duration. He complained of sensation of dullness and pressure in the upper part of the chest and could not lie flat in bed for long periods because of shortness of breath.

Physical examination revealed no obtainable blood pressure in the arms; pressure in the right leg was 152/104 and in the left leg was 150/100. The carotid pulse was not palpable. Indirect laryngoscopy revealed poor functioning of the right cord. There was no tracheal tug, and the thyroid was not palpable. There was widening of the

Fig. 15 (Case 5).—X-ray appearance Dec. 12, 1949.



mediastinal dullness. Venous congestion was noted in veins of both arms, especially on the left. Further history revealed that the patient had had some antisyphilitic treatment. The routine laboratory studies were within normal limits except for a 2+ Kahn reaction. Extensive x-ray studies (Fig. 12), including laminography and fluoroscopy with barium swallow, indicated that the mass was an aneurysm.

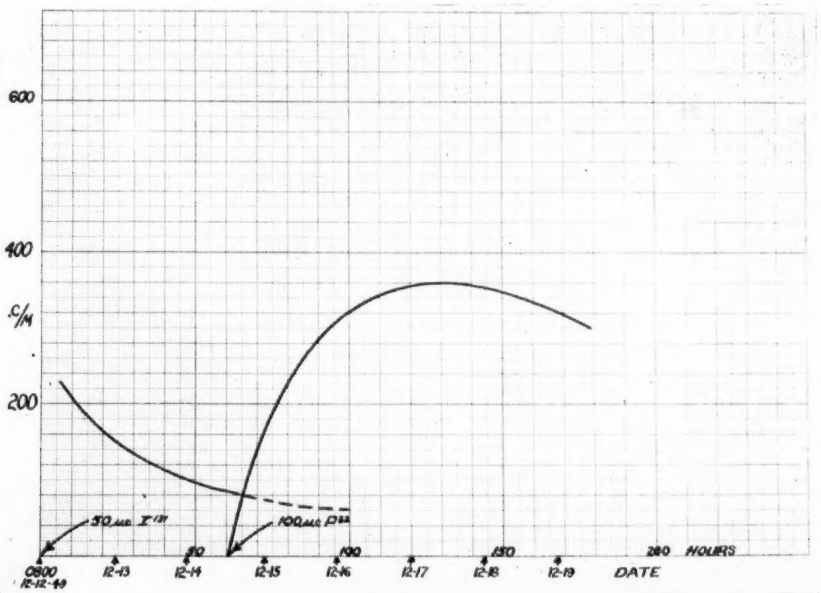
A radioactive iodine (I^{131}) tracer study indicated an extension of the thyroid behind the manubrium and upper portion of the sternum to the level of the second intercostal space (Fig. 13). With these two entities in mind, the patient was prepared for surgery.[20] A preoperative tracer dose of 100μc of I^{131} was administered Oct. 26, 1948. The Geiger-Mueller counter was taken to the operating room on Oct. 28, and the thyroid was outlined on the patient's skin prior to surgical preparation. The left chest was explored through the bed of the fourth rib. A large aneurysm of the aortic arch, approximately the size of a grapefruit, involving the left subclavian artery was demonstrated. Palpation around the anterior curvature of this aneurysm revealed soft tissue which had the gross appearance of a long tongue of the thyroid gland extending to the level of the second interspace. An attempt was made to demonstrate the surgical probe counter but failed because of a faulty counter tube; however, this procedure has been used successfully and has been reported elsewhere.‡ No attempt was made to correct the pathological condition existing because it was felt too hazardous, and the thorax was closed. The patient's postoperative course was without incident, and he was discharged on Nov. 4, 1948. Follow-up studies on this patient are unknown.

CASE 5.—A 39-year-old white woman was admitted to Harper Hospital Dec. 12, 1949. She had had a goiter for 18 years, first noted during her first pregnancy, but it had not bothered her until the last two years. She had recently noticed an intolerance to cold, weakness, increased perspiration, irritability, and some palpitations. She was fatigued, especially in the mornings. An x-ray examination at a local tuberculosis hospital had been performed in March, 1949 (Fig. 14). She continued to have vague pains and began to have itching sensations in her throat, along with a sense of pressure and sore throat.

Physical examination revealed a blood pressure of 142/90 and a pulse rate of 92. There was nodular swelling of both lobes of the thyroid, more prominent on the right; otherwise physical examination was negative. Routine laboratory studies were within normal limits. The basal metabolism rate on Dec. 13, 1949, was +10%.

‡ References 18 and 19.

Fig. 16 (Case 5).—Concentration curves for I^{131} and P^{32}, Dec. 12 to 19, 1949, showing negative result with I^{131}, positive result with P^{32}.



X-ray examination revealed a soft tissue mass, approximately 16 cm. in length, in the upper mediastinum on the right side, which extended from the midline toward the right for a distance of about 7 cm. (Fig. 15). It did not constrict or displace the trachea or the esophagus and was posterior to the upper level of the thyroid. From the x-ray study it appeared to be probably a lymphosarcoma or Hodgkin's disease, but a thyroid neoplasm could not be definitely excluded.

For further evaluation the patient was given a tracer dose of I^{131} on Dec. 12, 1949, followed by a P^{32} tracer study two days later. These tracer studies indicated that this mass most probably represented a rapidly proliferating malignancy,

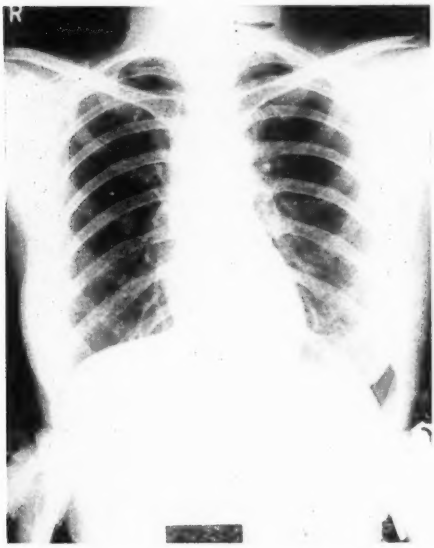


Fig. 17 (Case 5).—X-ray appearance Oct. 19, 1954.

possibly of the lymphoma group, overlying a retrosternal thyroid which had toxic manifestations and degenerated areas (Fig. 16). However, the possibility that the entire mass in the neck and retrosternal region represented a thyroid cancer could not be eliminated.

The patient was subsequently treated with deep x-ray therapy. Her response has been good. She was last seen in October, 1954, (Fig. 17) at which time she was asymptomatic. A pathological diagnosis has not been established, but the clinical diagnosis is lymphosarcoma of the mediastinum and a nontoxic nodular goiter with substernal extension.

SUMMARY AND CONCLUSIONS

Mediastinal tumors still present a challenge as to their preoperative diagnosis and more so as to their early detection so they may be treated in the proper manner. They have been well categorized as to their location and radiological characteristics. The treatment appears universal in agreement in that all should be surgically excised except for the lymphoma group, which is best managed with radiation therapy. In the series presented, where radioactive isotopes have been used preoperatively, 27 cases of thyroid origin and 28 cases of mediastinal tumors other than thyroid have been identified. Two hundred and eighty-eight cases of widening of the upper mediastinum have been traced to retrosternal extension of the thyroid. By accurate isotope technique we feel that the mediastinal lesions can be preoperatively categorized into three groups: (1) thyroid, (2) new growths with increased cellular activity, and (3) benign growths or anatomical abnormalities. The tracers can be used effectively to aid in planning the surgical approach to the lesion. It can be of benefit during the surgical procedure to locate involved tissue that may otherwise be overlooked. Since the predilection of the two isotopes seems specific and the physical capacity of the Geiger-Mueller counter to detect the presence of their radiations as to concentration in a given localization is physically accurate, the degree of accuracy depends upon interpretation of the end result. At present the interpretations have been gratifying, and, with continuing cooperation between the clinician and the radiological physicist, a standard diagnostic test may evolve, or at least a profound diagnostic aid.

Harper Hospital.

REFERENCES

1. Curreri, A. R., and Gale, J. W.: Mediastinal Tumors, Arch. Surg. **58**:797-818 (June) 1949.

2. Robbins, L. L.: Roentgenologic Features of Mediastinal Tumors, Radiology **43**:115-121 (Aug.) 1944.

3. Gurd, F. B.: Diagnosis of Lesions of Mediastina, S. Clin. North America **26**:282-291 (April) 1946.

4. Blades, B.: Mediastinal Tumors: Report of Cases Treated at Army Thoracic Surgery Centers in the United States, Ann. Surg. **123**:749-765 (May) 1946.

5. Sabiston, D. C., Jr., and Scott, H. W., Jr.: Primary Neoplasms and Cysts of the Mediastinum, Ann. Surg. **136**:777-797 (Nov.) 1952.

6. Lindskog, G. E., and Kausel, H. W.: Diagnostic and Therapeutic Problems in Benign Mediastinal Tumors, New England J. Med. **244**: 250-252 (Feb. 15) 1951.

7. Reynolds, L., and Leucutia, T.: Value of Roentgen Therapeutic Test Dose in Differential Diagnosis of Mediastinal Tumors, Am. J. Roentgenol. **48**:440-466 (Oct.) 1942.

8. Celis, A.; Pacheco, C. R., and del Castillo, H.: Angiocardiographic Diagnosis of Mediastinal Tumors with Special Reference to Aortic Aneurysms, Radiology **56**:31-38 (Jan.) 1951.

9. Thompson, J. V.: Collective Review: Mediastinal Tumors and Cysts, Internat. Abst. Surg. **84**: 195-221, 1947; in Surg., Gynec. & Obst., March, 1947.

10. Brewer, L. A., III, and Dolley, F. S.: Tumors of the Mediastinum: A Discussion of Diagnostic Procedure and Surgical Treatment Based on Experience with 44 Operated Cases, Am. Rev. Tuberc. **60**:419-438, 1949.

11. Mairer, H. C.: Diagnosis and Treatment of Mediastinal Tumors, S. Clin. North America **33**: 415-432, 1953.

12. Abbott, O. A.: Modern Methods of the Diagnosis and Treatment of Mediastinal Masses, South. Surg. **14**:101-110 (Feb.) 1948.

13. Silveus, E., and Adams, R.: Benign Mediastinal Tumors: A Report of 6 Cases with Analysis of Diagnostic Criteria and Advocation of Surgical Removal, S. Clin. North America **27**:596-604, 1947.

14. Abbott, O. A.; Hopkins, W. A., and Leigh, T. F.: Role of Angiocardiographic and Venography in Mediastinal and Paramediastinal Lesions, J. Thoracic Surg. **18**:869-891 (Dec.) 1949.

15. Heuer, G. J., and Andrus, W. DeW.: The Surgery of Mediastinal Tumors, Am. J. Surg. **50**: 146-212 (Oct.) 1940.

16. Corrigan, K. E., and Corrigan, H. H.: Use of Radioactive Phosphorus (P^{32}) as a Tracer Agent, J. Canad. A. Radiologists, to be published.

17. Levine, I., and Greenfield, H.: Mediastinal Pathology Discovered by Chance X-Ray of the Chest, New York J. Med. **54**:3199-3207 (Dec.) 1954.

18. Corrigan, K. E., and Hayden, H. S.: Diagnostic Studies with Radioactive Isotope Tracers, Radiology **59**:1-17 (July) 1952.

19. Dobyns, B. M.: Radioactive Iodine as an Adjunct to the Surgical Management of Diseases of the Thyroid, Surg., Gynec. & Obst. **93**:415-427 (Oct.) 1951.

20. Corrigan, K. E., and Hayden, H. S.: Failures, Flops and False Localizations in Tracer Technic, Radiology **60**:870-882 (June) 1953.

Exploratory Thoracotomy in Chronic Lymphadenitis of the Mediastinum

THOMAS R. LEECH, M.D.
CHARLES V. MECKSTROTH, M.D.
and
KARL P. KLASSEN, M.D., Columbus, Ohio

Chronic inflammatory processes of the mediastinal lymph nodes may produce constrictive, obstructive, or perforative lesions of the tracheobronchial tree, the esophagus, and the blood vessels of the mediastinum. Over a period of six years 33 such patients have come under our observation with involvement of one or more lymph nodes. Some were asymptomatic and were referred because of a mediastinal mass found on routine x-ray examination. Others presented severe symptoms, including hemoptysis, superior vena cava occlusion, and dysphagia, which, on occasion, could not be differentiated from those produced by malignant disease except by surgical intervention.

The anatomy of the mediastinal lymph nodes and their drainage patterns have been demonstrated by previous investigators.* These lymph nodes have been classified into groups according to their anatomical relations within the mediastinum. From a surgical standpoint these have been classified into three main groups: paratracheal, parabronchial, and paraesophageal. The paratracheal and paraesophageal lymph nodes can be subdivided into paracaval and paraaortic. Functionally they belong to the trachea and esophagus. The anterior mediastinal and paravertebral and intercostal lymph nodes will not be included because in our experience they do not produce symptoms.

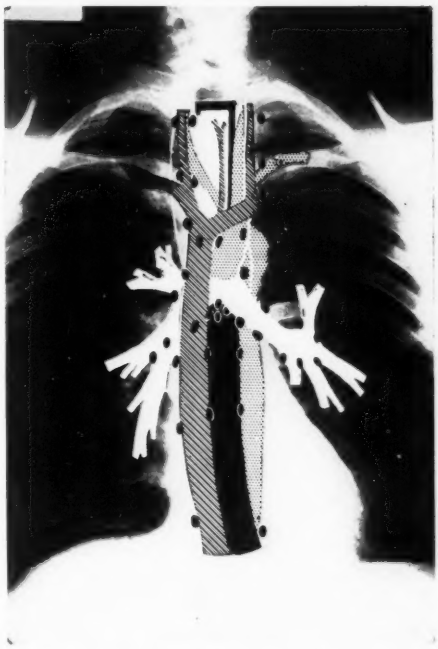


Fig. 1.—Diagram of the mediastinal lymph nodes and their relation to adjacent structures.

Our classification (Figs. 1 and 2) is based on findings in the cases presented and in thoracotomies performed for other conditions. The specific drainage of individual lobes is variable and depends upon previous involvement. In both acute and chronic pulmonary infections the process may be confined to a single group or may involve

Submitted for publication April 25, 1955.
Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Division of Thoracic Surgery, The Department of Surgery, the Ohio State University Medical Center.

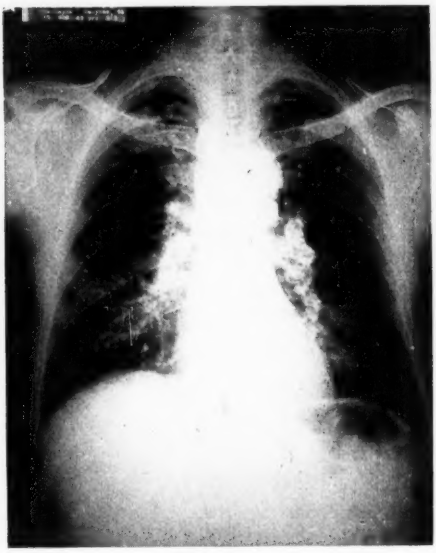
* References 1, 2, and 3.

Fig. 2.—Lateral projection of thorax showing position of the lymph nodes in relation to the mediastinum.

all groups of nodes in the mediastinum. Cross drainage also occurs, as has been established at surgery where small carcinomas of the lung have metastasized to the parabronchial lymph nodes of the contralateral side. In carcinoma of the esophagus, involvement of the paraesophageal lymph nodes is the rule and metastases to the paratracheal and parabronchial nodes occur early.

Generalized mediastinal lymph node involvement following inhalation of silicon dioxide is demonstrated in a roentgenogram shown in Figures 3 and 4. The inhaled particles are carried by the lymphatic drainage of the terminal bronchi and are transferred to the parabronchial lymph nodes of each particular segment. From here the particles are transported to the paratracheal and paraesophageal nodes. In a similar fashion the causative organisms of chronic mediastinal lymphadenitis are inhaled and carried to the mediastinal nodes. The primary parenchymal lesion, generally acquired in childhood, may resolve completely and leave no trace on subsequent x-ray films. Occasionally it persists with calcification of the parenchymal lesion and its draining lymph nodes. The acute process is associated with nodal enlargement which in time becomes either necrotic, with subsequent caseation and gradual liquefaction, or undergoes fibrotic contraction with calcification.

It is difficult to prove the exact causative organism of the lymphadenitis, since many



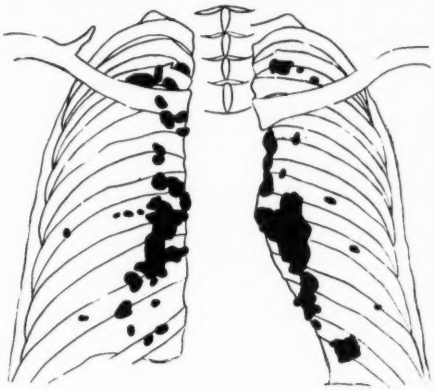


Fig. 3.—Calcification of the mediastinal lymph nodes in a patient with silicosis. Anteroposterior view.

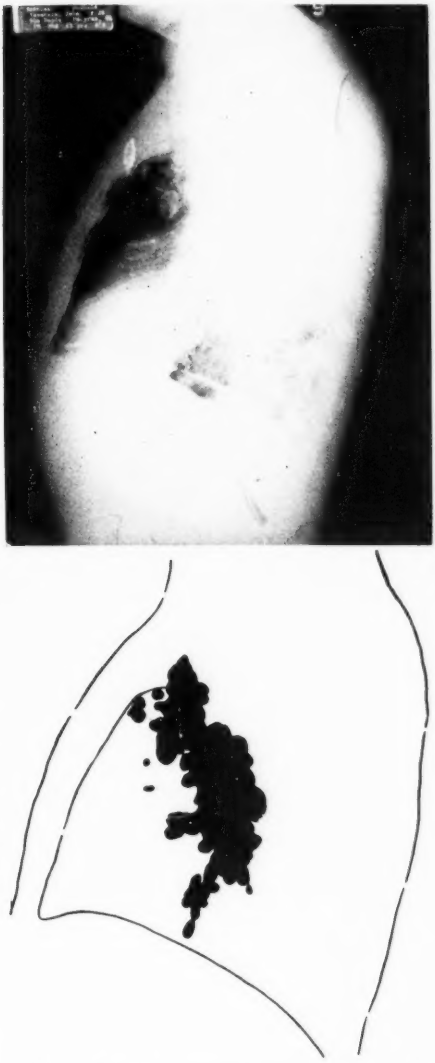


Fig. 4.—Lateral roentgenogram of patient with silicosis.

years elapse before the nodes are removed and studied. Skin tests for histoplasmosis and tuberculosis are assumed to be specific. Such sensitivity occasionally is lost. Histoplasmosis is endemic in Ohio and 60% of the adult population have a positive histoplasmin skin test. For this reason this test is of little value in determining the etiology of granulomatous lesions removed at surgery. The appearance of the removed nodes varies with the duration of the disease. The few young patients showed large, soft lesions which microscopically revealed giant cell proliferation with caseation typical of tuberculosis or histoplasmosis. The majority of specimens showed dense fibrosis, hyalinization, and calcification. It usually is impossible to distinguish between tuberculosis and histoplasmosis microscopically. Acid-fast bacilli were demonstrated by smear in one case. Subsequent cultures were negative. On only one occasion was Histoplasma capsulatum grown on culture. At no time were organisms seen on special stains of histological sections.

ANALYSIS

Analysis of the 33 cases of chronic mediastinal lymphadenitis is shown in Tables 1, 2, and 3. The classification is based on the location of the nodes, and some anatomical overlapping occurs.

Parabronchial Lymph Nodes

In 12 patients the offending lymph node was considered parabronchial in location. Six of these nodes were symptomatic, hemoptysis being the complaint of four pa-

Fig. 5 (Case 3).—Parabronchial lymphadenitis due to Histoplasmosis capsulatum.

TABLE 1.—*Parabronchial Lymphadenitis*

Case	Age	Sex	Symptoms	X-Ray Findings	Findings at Surgery	Treatment
1	58	F	Hemoptysis	Rt. hilar calcification, partial bronchial block	Pedunculated intrabronchial calcified node	Excision by bronchotomy
2	53	M	Hemoptysis	Rt. hilar calcification, partial bronchial block	Bronchial compression	Excision by bronchotomy
3	45	M	Cough	Lt. hilar mass, 4 × 6 cm.	Lymphadenopathy, H. capsulatum grown	Excision
4	53	M	None	Calcified subcarinal mass, 6 cm.	No surgery	None
5	51	M	Hemoptysis	Rt. hilar node	Lymphadenopathy	Excision
6	51	F	None	Calcified rt. hilar mass, 4 cm.	Calcified node	Excision
7	59	F	None	Calcified rt. hilar mass, 3 cm.	Calcified node	Excision
8	30	M	None	Rt. hilar mass, 6 cm.	Caseous nodes	Excision
9	30	F	None	Calcified carinal node, 6 cm.	Calcified node with liquefaction	Excision
10	59	F	None	Rt. hilar calcified mass, 5 cm.	Calcified node with liquefaction	Excision
11	35	M	Wheezing	Lt. hilar mass, bronchial compression	Stony, thrombosed pulmonary veins	Exploration *
12	66	F	Hoarseness	Calcified nodes	Lt. recurrent laryngeal nerve involvement by calcified node	.....

* Death due to blood loss.

TABLE 2.—*Paratracheal Lymphadenitis*

Case	Age	Sex	Symptoms	X-Ray Findings	Findings at Surgery	Treatment
13	17	M	None	Rt. sup. mediastinal mass, 5 cm.	Soft tumor mass	Excision
14	12	M	Cough	Rt. sup. mediastinal mass, 3 cm.	Soft tumor mass, Mycobacterium tuberculosis on smear	Excision
15	8	M	Cough	Rt. sup. mediastinal mass, 6 cm.	Large lymph node	Biopsy
16	34	F	Cough	Rt. sup. mediastinal calcified mass, 4 cm.	Calcified caseous node	Excision
17	44	M	Pain in chest	Rt. sup. mediastinal calcified mass, 4 cm.	Calcified caseous node	Excision
18	27	F	None	Rt. sup. mediastinal calcified mass, 4 cm.	Calcified caseous node	Excision
19	27	F	Pain	Rt. sup. mediastinal calcified mass, 6 cm.	Calcified caseous node	Excision
20	26	M	Sup. vena cava syndrome	Rt. sup. mediastinal calcified node, 0.4 cm.	Thrombosis of sup. vena cava	Aortic homograft
21	32	M	Sup. vena cava syndrome	Rt. sup. mediastinal calcified node, 1 cm.	Thrombosis of sup. vena cava	Biopsy
22	26	M	Sup. vena cava syndrome	Rt. sup. mediastinal calcified node, 0.5 cm.	Thrombosis of sup. vena cava	Femoral vein graft
23	47	M	Sup. vena cava syndrome	Calcified thrombus sup. vena cava	Thrombosis of sup. vena cava	Biopsy
24	37	M	Sup. vena cava syndrome	Calcified node sup. mediastinum 0.5 cm.	Thrombosis of sup. vena cava	Biopsy

TABLE 3.—*Paraesophageal Lymphadenitis*

Case	Age	Sex	Symptoms	X-Ray Findings	Findings at Surgery	Treatment
25	61	M	Dysphagia	Intraesophageal pedunculated tumor	Intraesophageal pedunculated caseous nodes	Excision of node, esophageal repair
26	52	M	Cough on swallowing	Rt. bronchoesophageal fistula	Bronchoesophageal fistula through caseous node	Excision of node, bronchial and esophageal repair
27	70	M	Dysphagia	Megaesophagus	Inflammatory stricture by caseous node	Esophagogastrostomy
28	71	M	Dysphagia	Traction diverticulum mid-esophagus	Esophageal carcinoma above diverticulum	Biopsy
29	57	F	None	Traction diverticulum mid-esophagus	No surgery	None
30	60	F	None	Traction diverticulum mid-esophagus	No surgery	None
31	39	F	None	Traction diverticulum mid-esophagus	No surgery	None
32	..	F	None	Traction diverticulum mid-esophagus	No surgery	None
33	..	M	None	Traction diverticulum mid-esophagus	No surgery	None

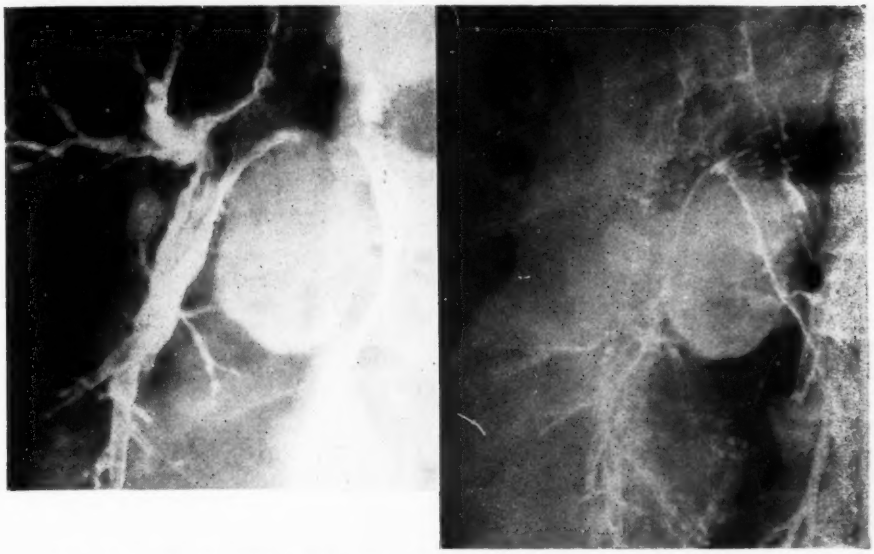


Fig. 6.—Minimal bronchial and esophageal distortion from calcified subcarinal lymph node.

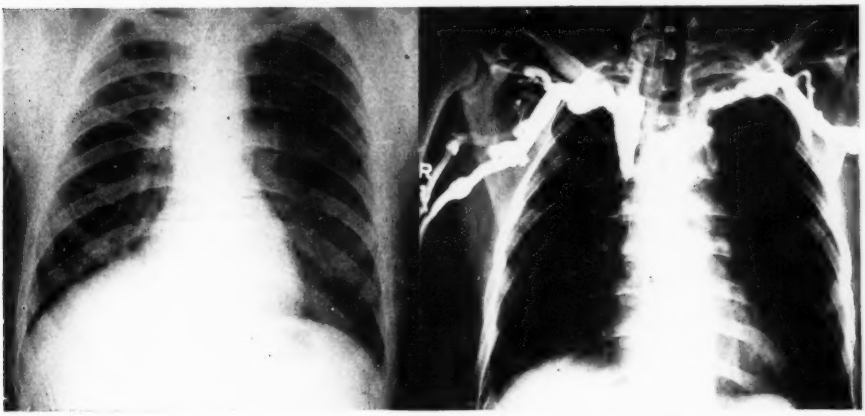


Fig. 7 (Case 22).—Small calcified paratracheal lymph node producing complete superior vena cava occlusion.

tients. Others were referred for investigation because of an asymptomatic mass in the hilar region. In all these patients bronchography and bronchoscopy were performed, both being of definite diagnostic value. The deformity of the membranous portion of the bronchus was demonstrated by bronchography in four patients, and in two of these endoscopic biopsy specimens from an intraluminal polypoid mass showed a chronic inflammatory lesion characteristic of granuloma compatible with either tuberculosis or histoplasmosis. In eight patients dense calcification was present on x-ray. In Case 12, the patient with laryngeal nerve paralysis, calcified nodes were present throughout the mediastinum and both hilar regions.

Lymphoma was suspected in Case 3 (Fig. 5), but the removed specimen showed a

granulomatous lesion. In this patient tuberculosis and histoplasmosis skin tests were positive. The exact etiology was proved by culture to be positive for H. capsulatum. Case 4 had been observed for four years. The patient was asymptomatic, and, although there was some distortion of the esophagus and widening of the carina (Fig. 6), surgical removal of this calcified lymph node did not appear warranted. Malignancy was suspected in Case 11, since bronchography revealed narrowing of the left main bronchus. At surgery extensive peribronchial and pleural venous collateral circulation due to occlusion of both pulmonary veins was found. The dissection was extremely difficult, and pneumonectomy could not be carried out. The patient died of blood loss, and this was the only mortality in this series. Culture showed Actinomycosis due to Nocardia.

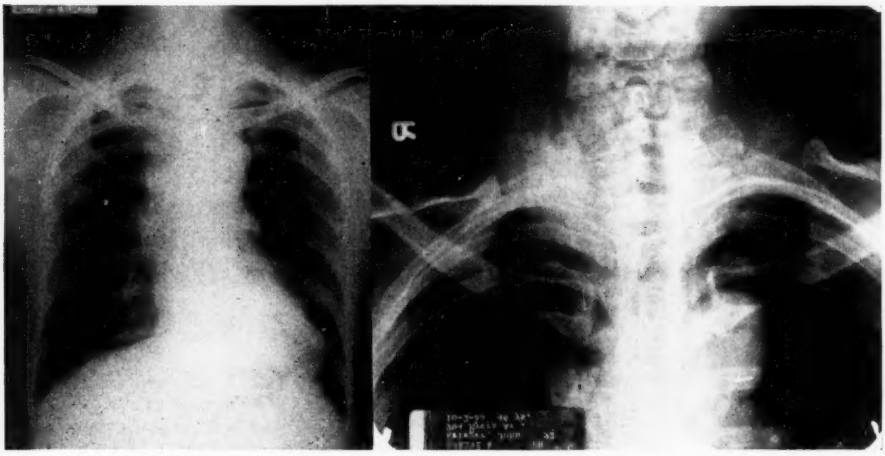


Fig. 8 (Case 23).—Ossified thrombus of superior vena cava and jugular vein.

Paratracheal Lymph Nodes

Twelve patients presented involvement of only the right paratracheal lymph node group. In seven, symptoms were mild and usually the patients had no complaints until the presence of a mass had been demonstrated on routine x-ray examination. In two of these the knowledge of the presence of a "tumor" led to severe pain in the chest which could not be explained by segmental nerve innervation. Three patients, aged 8, 12, and 17 years, were considered to have lymphomas, and thoracotomy was performed because of the presence of large noncalcified mediastinal masses. No definite symptoms were present in these patients, and the lymph nodes were excised only for diagnosis. Microscopic studies in all three showed granulomatous lesions compatible with either tuberculosis or histoplasmosis. Organisms could not be grown from these lymph nodes.

Five patients presented superior vena cava occlusion symptoms which developed over several years. Venograms demonstrated total block of the superior vena cava in all patients (Fig. 7).

Operative findings in these cases were similar. There was fibrotic reaction adjacent to a small calcified lymph node, with concentric contraction at this point and distal thrombosis of the vena cava. In Case 23 there were complete calcification and ossification of the superior vena cava extending into the jugular vein (Fig. 8). There was no evidence of recanalization of the thrombosed vena cava in any of these five patients. Case 22 was treated with a femoral vein graft between the azygos vein and proximal vena cava. Although patency has been demonstrated for

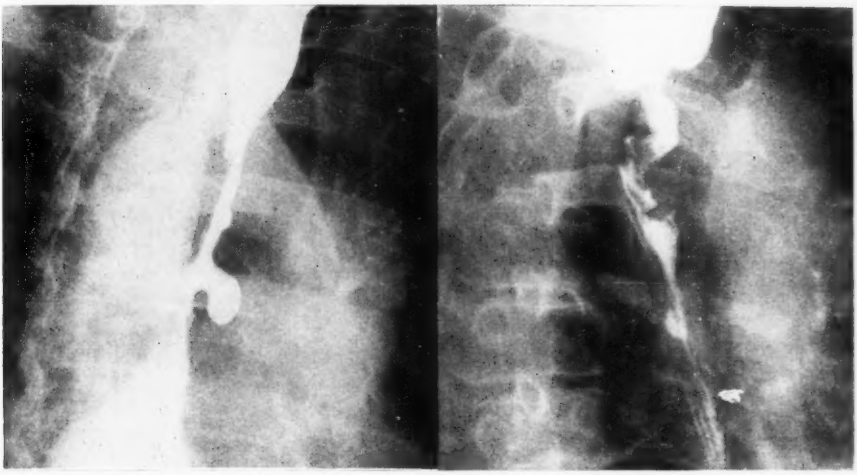


Fig. 9 (Case 27).—Traction diverticulum of midesophagus with irregularity of proximal esophagus subsequently proved to be a carcinoma as shown in roentgenogram on right taken six months later.

Fig. 10 (Case 26).—Demonstration of bronchoesophageal fistula by lipiodol swallow.

over four years, the venous pressures in the upper extremity have not returned to normal. In Patient 20, where an aortic homograft was used, thrombosis occurred two weeks following surgery.

Paraesophageal Lymph Nodes

The paraesophageal lesions are the result of inflammation passing through the paratracheal lymph nodes. Five patients had traction diverticula demonstrated by x-ray examination. None of these patients complained of dysphagia, and surgical intervention was not considered, since there was no narrowing of the esophageal lumen and the diverticulum emptied adequately without producing alteration in the mechanism of swallowing.

One additional patient with traction diverticulum was seen who developed progressive difficulty in swallowing over a period of six months. His difficulty was thought due to the presence of the traction diverticulum shown in Figure 9, and no additional studies were made. Six months following the initial examination, barium study showed the presence of a far-advanced carcinoma of the upper esophagus, which was proved later by esophageal biopsy. Examination of the previous film shows the early changes in the esophageal lumen due to the carcinoma.

In Patient 25, a preoperative diagnosis of pedunculated leiomyoma of the esophagus was made on the basis of barium study. Biopsy of this tumor proved it to be a granulomatous lymph node. At surgery simple excision of this pedunculated tumor with primary closure of the esophagus was accomplished, with complete relief of obstructive symptoms. Microscopic sections showed a granuloma typical of tuberculosis. Patient 26 exhibited a typical example of bronchoesophageal fistula with dramatic onset of symptoms. X-ray studies (Fig. 10) demonstrated communication between the esophagus and the posterior portion of the right main bronchus. The fistulous tract and involved lymph node were excised. Repair of the membranous portion of the bronchus and closure of the esophagus resulted in cure.

In Patient 27, progressive obstruction of the esophagus had been present for five years. A megaesophagus developed proximal to the obstruction, and esophageal biopsy was suggestive of carcinoma. At surgery no tumor could be demonstrated. Exploratory thoracotomy revealed a constricting lesion of the esophagus contiguous with a granulomatous lymph node. Resection of the distal esophagus and esophagogastrostomy resulted in relief of the patient's symptoms.

COMMENT

A noncalcified mediastinal mass found on routine x-ray examination is a surgical problem in that a diagnosis of lymphadenitis cannot be made without thoracotomy and biopsy. Skin tests are not specific, and peripheral blood studies, as well as bone marrow examination, may not reveal the exact nature of the lesion. Bronchoscopy and bronchography are valuable in determining the amount of bronchial involvement.

A large calcified mediastinal lymph node presenting no symptoms does not require surgical intervention. Patients with such lesions should be reassured, since too much stress placed upon the presence of these tumors may lead to subjective symptoms.

Patients presenting symptoms due to compression, obstruction, or constriction of the adjacent mediastinal structures should have definitive surgery for correction of the abnormality. Results of by-passing procedures for the relief of superior vena cava occlusion have thus far been disappointing. The elevated venous pressure of the head and upper extremities was well tolerated by our patients. Until grafting procedures are more successful, surgery for this condition appears unjustifiable.

In tracheal and bronchial compression, surgery becomes necessary for the purpose of exact diagnosis and for relief of the compression. Early surgical intervention may prevent irreparable damage to distal bronchopulmonary tissue.

The surgical treatment of enlarged mediastinal lymph nodes, either calcified or noncalcified, may present considerable technical difficulties. Because of marked pericapsular reaction, these nodes are firmly adherent to adjacent structures, such as the vena cava, trachea, bronchus, or esophagus. Attempts at complete removal may lead to disastrous sequelae unless caution is observed. In lymphadenitis without calcification, only biopsy of the lesion is advisable, while in those containing a large amount of necrotic amorphous material, excision of the major portion of the tumor should be performed, leaving behind the fibrous wall, which is firmly adherent to the adjacent structures. In none of these patients has there been dissemination of infection by fragmentation of

the tumor or by leaving a portion of the wall of the capsule.

SUMMARY

A series of 33 patients has been presented to illustrate the surgical significance of chronic mediastinal lymphadenitis. While some of the lesions were found on routine x-ray examination of asymptomatic patients, the majority produced symptoms suggestive of malignancy. Exploratory thoracotomy was carried out for the purpose both of diagnosis and of the correction of abnormalities produced by chronic lymphadenitis of the mediastinum.

Ohio State University Medical Center
Columbus, Ohio

REFERENCES

1. Sukiennikow, W.: Topographische Anatomie der bronchialen und trachealen Lymphdrüsen, Berl. klin. Wchnschr. **40**:316, 1903.

2. Rouvière, H.: Anatomy of the Human Lymphatic System: A Compendium Translated from the Original "Anatomie des lymphatiques de l'homme" and Rearranged for the Use of Students and Practitioners by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938; Anatomie des lymphatiques de l'homme, Paris, Masson & Cie, 1932.

3. Miller, W. S.: The Lung, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1947.

4. Klassen, K. P.; Andrews, N. C., and Curtis, G. M.: Diagnosis and Treatment of Superior-Vena-Cava Obstruction, A. M. A. Arch. Surg. **63**:311-325 (Sept.) 1951.

DISCUSSION

ON PAPERS BY DRS. SWEDENBURG, TUTTLE, AND CORRIGAN AND LEECH, MECKSTROTH, AND KLASSEN

DR. W. E. ADAMS, Chicago: I have enjoyed very much hearing these two papers. I think they pointed up two problems to which in the past we have been unable to get the answers which we would prefer prior to exploration.

As regards the first paper, it seems to me that the discrepancy between the reports today and the reports in the literature point up probably two facts. One is the difference in pathological material with which they had to deal, and the second is the means of investigation of the problem.

I think it is obvious that when one has equipment for studying lesions which will absorb these radioactive materials much information can be gained to aid us in differential diagnosis.

The inactive lesions of the thyroid pushing down beneath the sternum, which will not absorb radioactive isotopes, obviously will not show us a definite diagnosis before exploration. Of course, we have other means than these, viz., x-ray examinations for making at least a working diagnosis, and in the past those have been fairly accurate in a high percentage of cases.

In addition to the thyroids which are active or inactive, we have the group of carcinoma of the thyroid which at times extends down beneath the sternum. In these cases methods of scanning the lesion after the use of radioactive isotopes have been of particular value, especially after the primary tumor has been removed from the neck.

I should like to read into this discussion a review given me by one of our staff members, Dr. Eshell, on the results of a study of approximately 500 thyroids operated on during the past four years.

For this study a scintillating scanning device was used, similar to that which was discussed here in the previous paper. There were eight substernal goiters in this series, all of which were nonfunctioning. The routine uptake study of radioactive iodine was of no diagnostic value in any of the eight patients. However, scanning with a scintillation scanner allowed a diagnosis in all but one.

In 22 patients with carcinoma of the thyroid with substernal extension, both the radioactive iodine uptake over the extension of the tumor and the scanning were diagnostic in 20 out of the 22 cases.

As you know, there has been work with an additional substance in addition to the two mentioned today, viz., the iodinated albumin, but up to the present time I understand that has been of relatively little value in diagnosing these conditions.

Taking everything into consideration, it would appear that as time goes on we may have at our command a means of differentiation in these superior mediastinal tumors which will aid us greatly in planning therapy.

Regarding the second paper, I think the authors have brought before us another problem, and the presentation of the x-rays shows the means which at times are very helpful in differential diagnosis.

In this particular Central States area we are seeing a considerable amount of histoplasmosis. This may involve the mediastinum as well as the lungs.

[Slide] I think you can see this calcified mass in this slide better on the tomograph, but it is seen also in the other two x-rays. This calcified mass lay adjacent to the superior vena cava. I point this out particularly because in the removal of these masses through the inflammation that has been

created previously they may involve the wall of large vessels, particularly veins, and may present a real problem as regards injury to the vessel during its removal.

[Slide] Here is a similar lesion seen at this point in a girl of 17. In both cases these lesions were picked up on routine examination. Neither of the patients had had any symptoms.

[Slide] Here is an infrared photograph of a patient who has complete obstruction to the superior vena cava by one of these masses resulting from a low-grade inflammation.

[Slide] This shows one similar to the one you have seen previously, with complete obstruction to the superior vena cava by one of these lesions.

Over a period of time compensation by a flow of blood returned to the heart around through the inferior vena cava takes place and many of these patients (if they are occupied in a sedentary type of work) can get along with a complete occlusion of the superior vena cava. We have followed two such patients over the past 7 to 10 years. Although at the beginning, while they were becoming compensated for this obstruction, they had symptoms such as severe headache and dizziness, after this compensation had become more complete they were able to get along with little difficulty.

I want to congratulate the authors of both of these papers for bringing these important problems to us and for presenting them in the excellent manner they have done.

DR. JACOB BERMAN, Indianapolis: Mediastinal disease is often difficult to diagnose, and its exact nature is even more baffling at times. The papers by Dr. Swedenburg, Tuttle, and Corrigan and Drs. Leech, Meckstroth, and Klassen are very timely.

Last summer Dr. Herbert Judy, my research resident, and I studied 169 cases of mediastinal disease. The most important result of our study was the discovery that extraluminal pathology was often not suspected or missed completely, as proved subsequently by operation. This finding stimulated me to search for additional aids in preoperative diagnoses.

With the aid of Dr. Tosick, our radiologist, and Drs. Judy, Levene, and Mori we developed a method of visualizing the mediastinal spaces. We have termed this procedure extraluminal mediastinography. By this device we can produce a silhouette of the mediastinum, and then by taking films from various angles we are able to obtain a diagnosis of the position and usually the probable nature of the disease. When this device is used in conjunction with other methods, such as those described by Dr. Tuttle, the accuracy of diagnosis is greatly increased and the surgeon may plan his operative procedure more correctly.

Extraluminal mediastinography may yield the following pertinent information:

1. The contour of the normal mediastinum.
2. The visualization of tracheal or bronchial tears.
3. The presence of extraluminal extensions of intraluminal disease within the bronchial tree, esophagus, or blood vessels.
4. The degree of extraluminal pressure causing the defect to appear in the intraluminal shadow.
5. The extent and location of mediastinal lesions which have no intraluminal connections.
6. The more accurate interpretation of shadows which begin within the lungs or adjacent organs.
7. The demonstration of communication beneath the diaphragm and delineation of areas occupied by the pancreas, kidneys, and the adrenals, thereby revealing so-called hidden carcinoma or other disease processes. Indeed, perirenography and retroperitoneography is probably quicker, safer, and more accurate than air injection.

I regret that I forgot to bring my slides with me, but our papers will appear in the March issue of the *Journal of the Indiana Medical Association* as a preliminary report and in the April issue of the *Western Journal of Surgery, Obstetrics and Gynecology*. Illustrations of the normal and abnormal mediastinum are shown; so I shall not take time to describe them here.

We were desirous of ascertaining the size of the mediastinal space in humans; therefore, we injected methylene blue solution into the anterior and the posterior mediastinum of fresh autopsy specimens. The superior mediastinal space holds roughly 75 to 100 cc., the anterior or previsceral space 50 cc., and the posterior or retrovisceral compartment 100 to 150 cc.

A 35% solution of iodopyracet (Diodrast) was injected into the mediastinal spaces of selected patients suspected of having mediastinal lesions. Skin tests for sensitivity were done in all cases. There were no significant changes in pulse, blood pressure, or electrocardiographic tracings after injections, and the patients tolerated the material extremely well. However, some pain was experienced about 10 minutes after the injection. The superior mediastinum is entered as follows: the skin over the suprasternal notch is anesthetized with 0.5% procaine hydrochloride (Novocaine). A No. 18 guage 4 in. spinal needle which has been slightly bent is inserted about midway between the trachea and sternum. The plunger of the syringe is pulled back to be sure that the needle is not in a blood vessel and then 75 cc., of a 35% solution of iodopyracet is injected rather slowly. X-ray examinations in various positions are made im-

mediately after injection, then every half-hour for six exposures. The material is best seen in the half-hour films and is completely absorbed in about three hours.

The posterior mediastinal space is clearly visualized by injecting 100 cc. of a 35% iodopyracet solution. This is accomplished by introducing a No. 18 guage spinal needle anterior to the sternomastoid muscle on either side until the vertebral column is reached, then pulling slightly forward and directing the needle medially into the prevertebral space or retrovisceral compartment.

The anterior space is injected with 50 cc. of 35% iodopyracet with a curved No. 18 needle immediately behind the sternum. Films of the kidneys, ureters, and bladder showed excellent visualization of these structures due to the rapid absorption and excretion of the iodopyracet.

There have been no complications with this method. It has revealed the spaces in silhouette, and when more than one space was injected simultaneously the silhouette of the solid organ or lesion was outlined. We have learned a great deal about the anatomy of the spaces, and we have been able to plan our operations more expertly with the aid of this diagnostic means.

This method may also be useful for perirenography and retroperitoneography in revealing so-called hidden carcinoma or other lesions of the kidney, pancreas, or other retroperitoneal organs.

DR. AUGUST F. JONAS, San Francisco: In relation to the diagnosis of obscure lesions within the chest, for the past year we have been employing the method of Dwight Harkin, of Boston, which is really an extension of a scalene fat pad biopsy originally described by Dr. Albert Danield, simply done through a small incision over the medial third of the clavicle.

This reconnaissance of cervical and upper mediastinal lymph nodes we combined with bronchoscopy and with scalene fat biopsy as a diagnostic package, all done under local anesthesia at the same time. It is useful in determining operability in carcinoma of the lung or in mediastinal problems of obscure origin. We believe it has proved distinctly valuable.

During the past two years we have had 65 cases in whom the diagnosis was in doubt and in whom operability had to be determined. None of these had palpable lymph nodes in the neck or the supraclavicular area, but, by a small incision and removal of the supraclavicular fat pad, and by the passing of a finger downward alongside the apex of the lung and pushing it to one side, and without creating pneumothorax, and feeling nodes alongside the trachea down to the arch or down to the great vessels, and when necessary enucleating them or removing them through a lighted Jackson laryngoscope, we have been able to secure positive diagnoses in about one-third of these cases.

In 65 cases which were subjected to such a procedure, none of them having palpable nodes, we were able to prove that carcinoma was present in 15 of them, and 7 more showed sarcoid, Hodgkin's disease, or granulomata. Thus, in 22 cases out of the 65 we achieved a precise diagnosis without subjecting the patient to a formal thoracotomy.

DR. ELMER R. MAURER, Cincinnati: I should like to limit my comments to the paper presented by Dr Leech on chronic mediastinal lymphadenitis.

Approximately two and a half years ago I reported in the *Journal of Thoracic Surgery* on the serious significance of calcified parabronchial and paratracheal lymph nodes. They are serious for several reasons.

First of all, the pulmonary lesions produced by these obstructing calcified lymph nodes can simulate clinically and radiographically in all respects primary carcinoma of the lung. In those instances where one has an obvious pulmonary lesion, regardless of its configuration or nature by x-ray, additional studies, such as planography or Bucky films, would appear to be indicated, and if a calcified node is encountered proximally then the comments I will make shortly would be pertinent.

Almost invariably when a surgeon approaches elective pulmonary resection surgery, if he encounters on the x-ray numerous calcified lymph nodes about the bronchi or in the mediastinum, he can anticipate a tedious, time-consuming, complicated dissection associated with an appreciable oozing of blood as a result of the dense deposits of scar tissue, the increased vascularity of the field, and the almost complete obliteration of the normal planes of dissection which are incident to the original infection that caused the nodes to enlarge and calcify.

Often the surgeon may be forced into a much more radical operation than he anticipated before surgery, because of actual invasion of a lobar or main-stem bronchus and sometimes even the trachea by a large calcified lymph node far proximal to the line of amputation which was originally planned.

I think this is a very important subject that has received too little discussion in the past, and I am particularly grateful to Dr. Leech and his associates for bringing it to our attention today.

DR. HIRAM T. LANGSTON, Riverside, Ill.: I wish to make just one brief comment.

You have heard quite an array of diagnostic maneuvers exposed here today with the idea of trying to ascertain the nature of some of these mediastinal masses. An observation has come to me recently—and it is still incomplete but quite intriguing—having to do with the question of approach.

There are those who go through the neck; there are those who go through the chest; there are those who go through some combination. Simply enough, if you will have your patient carry out a Valsalva maneuver you will be surprised at the number and size of masses that will disappear from the mediastinum. Those that do disappear by the simple expedient of a Valsalva maneuver are very likely to be removable through a cervical approach.

I mention one point of caution: you should confirm this with a film, because a cervical thyroid mass may appear and become more palpable under these circumstances, but the point of interest is whether the mediastinal mass disappears under these circumstances.

DR. ROBERT D. SWEDENBURG, Detroit: I wish to thank the discussants for their interest in this paper. I have nothing more to add except that I failed to point out in the presentation that these cases I presented were primarily confusing problems, and they all had rather extensive studies. A majority of their physical findings were negative.

It might be emphasized that the symptoms and signs occur very late in many of these lesions and are of little diagnostic help. It might be well also to point out that there is little relationship between the "uptake" study and the type of tracer study reported here.

DR. THOMAS R. LEECH, Columbus, Ohio: I should like to thank the discussants for their information and ideas which they have added to the paper.

I should like to add that we find it extremely difficult to establish an accurate etiology in any of our cases. We presented those that show no parenchymal lesions in the lung—just lesions in the mediastinum. In only three of the cases was an accurate etiological factor found. In one, acid-fast bacilli were found on smear, in another Histoplasma capsulatum was demonstrated by culture, and Actinomycetes were found in the third.

The Influence of Stress upon Liver Function in Obstructive Jaundice

CHARLES A. MACGREGOR, M.D.
JOSEPH B. GRIFFITH, M.D.
and
GORDON A. MUNRO, M.D., Denver

Liver failure and death following surgery on patients with obstructive jaundice are not uncommon. Such a postoperative course is usually manifested in part by a febrile coma, a rising level of serum bilirubin, and a falling level of cholesterol esters and albumin. There can be little doubt that the operation in some way has directly influenced the course of the patient. The specific etiological details, however, are rather obscure. The relative importance of such details is difficult to assess from clinical cases. Some of these factors are the impaired liver function existing preoperatively, the anesthesia, the nonspecific stress of the operation and coincident hypoxia or sepsis.

In an effort to clarify the problem by experimental observations the authors have undertaken a series of studies to evaluate the relative importance of each factor. A detailed and thorough analysis of the course of liver function in dogs with simple uncomplicated obstructive jaundice has recently been reported.[1] The study to be described in this report concerns the influence of stress with and without anesthesia upon liver function in the dog with obstructive jaundice.

Received for publication April 25, 1955.

From the Department of Surgery, University of Colorado School of Medicine.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

Supported by a grant from the Public Health Service, National Institute of Health, Bethesda, Md.

HISTORICAL BACKGROUND

A. Reaction of the Normal Liver to Various Forms of Stress.—In the past few years there has been a rather marked rise in interest concerning the reaction of the liver to various forms of stress.

Fine,[2] in 1947, in studying liver function in dogs with advanced hemorrhagic shock showed that sulfobromophthalein sodium (Bromsulphalein) excretion is impaired and that the prothrombin time was increased. Inconsistent microscopic hepatic degeneration, both diffuse and focal, was described by Moon [3] in 1948 in a study of secondary shock. Levin [4] in 1949 described fatty infiltration as an effect of stress (cold and severe exertion) upon the liver of the mouse. Also in 1949 Gillman and Gillman,[5] in a study of the effects of shock on the liver function of dogs, described an increased excretion of galactose in amounts far in excess of that of control dogs. They also noted an increase in the prothrombin time but little change in the sulfobromophthalein excretion and the level of serum phosphatase. A more recent study of the effect of hemorrhagic shock in dogs by Frank,[6] in 1953, reports an increase in blood sugar concentration, a decrease in liver glycogen, a delay in regeneration of plasma albumin, prothrombin, and fibrinogen, an impairment in the galactose tolerance test, and little change in the excretion of sulfobromophthalein.

The results of liver function tests have been studied by Fairlie and associates [7] before anesthesia and on the first, third, and fifth day after operation in 34 patients who underwent operation on the lower abdomen and legs. The patients had neither history nor clinical evidence of liver or other systemic disease. The liver function tests included the sulfobromophthalein-excretion test, the intravenous hippuric acid test, and

determinations of the serum bilirubin, the plasma prothrombin time, the serum alkaline phosphatase, and the serum cholesterol and cholesterol esters. Abnormalities were present after operation in almost every case. The sulfobromophthalein retention was the most striking. It was elevated in 18 of the 34 cases at some point in the postoperative period, at times reaching 15 to 30% retention. Fairlie and co-workers concluded that there is no significant difference among ether, cyclopropane, and spinal anesthesia in their effect on the normal liver. They also stated that it is probable that the changes in liver function observed represent a part of the organism's total reaction to stress rather than a toxic effect of the anesthetic agents employed.

B. Reaction of the Abnormal Liver to Various Forms of Stress.—French and associates,[8] in 1952, studied the influence of shunt operations upon the liver function of 15 patients with mild (compensated) liver disease and of 18 patients with moderate liver disease due to portal hypertension. There were extensive changes in all the liver function tests used. The patients with mild liver disease showed sulfobromophthalein retention peaks ranging usually from 18% to 48%, while with the moderate liver disease the spread was from 28% to 66% retention. Rises in serum bilirubin, urine urobilinogen, prothrombin time, and serum alkaline phosphatase were frequent and much greater than those seen in the absence of liver disease. These authors stated that there was no discernible effect of anesthesia upon the degree or duration of postoperative liver function test abnormalities. They concluded that the changes observed were probably a part of the pattern of response by the liver to severe nonspecific stress.

C. Reaction of the Normal Liver to Corticotropin.—In describing the effect of corticotropin (ACTH) (40 mg. daily for 4 days) in a normal subject, Forsham and associates [9] reported a decrease in serum protein and an increase in the fasting blood sugar.

Sayers and associates,[10] in 1949, reported that the electrophoretic distribution of serum proteins remained unchanged in two normal subjects after the intravenous administration of 100 mg. of corticotropin as a single dose. In the same year Thorn and Forsham [11] showed that the administration of 40 mg. of corticotropin (10 mg. every six hours) for four days resulted in an increase in the fasting blood sugar, a decrease in serum inorganic phosphorus, and an increase in liver glycogen as determined by liver biopsy. In a study of 18 normal patients receiving corticotropin over an average of 48 days, Adlersberg and associates [12] in 1950 reported an elevation of total serum cholesterol with a concomitant elevation of esterified cholesterol and phospholipid. The increase averaged 33%. Sprague and associates [13] in 1950 also emphasized the diabetogenic tendency of corticotropin in the normal human. From a study of 17 patients with rheumatoid arthritis who received 100 mg. of corticotropin daily for 6 to 18 days, Sprague and associates [14] also reported that the serum zinc sulfate turbidity (a measure of serum gamma globulin) was decreased but there was no consistent pattern of change in the serum alkaline phosphatase.

Conn and associates [15] found that when normal humans were given 68 mg. of corticotropin daily for six days there was a sharp decrease in the total serum cholesterol. They observed that 85% of the decrease in total cholesterol was due to the decrease in the ester fraction. They concluded that, on the basis of the assumption that esterified cholesterol of the serum is drawn upon during periods of acute or chronic stress as a readily available precursor with which to satisfy the increased demand for corticosteroid production, diminished hepatic function may assume the role of a limiting factor in the total response of the cortex to stimulation.

A fall in the serum globulin from 10.2 gm. to 4.8 gm. per 100 cc. in a patient with multiple myeloma who was given 20 mg. of corticotropin every 6 hours for 20 days was reported by Thorn [16] in 1950. He also noted a rise in the serum alkaline phosphatase from 3.0 Bodansky units before treatment to 6.8 at the end of therapy.

D. Reaction of the Abnormal Liver to Corticotropin.—Havens and associates [17] in 1952 in a study of 15 patients with cirrhosis and 3 patients with convalescent hepatitis who were treated with 80 to 100 mg. of corticotropin daily from 10 to 27 days, noted a fall in circulating eosinophiles but only slight alterations in the tests of liver function. These included the serum bilirubin, sulfobromophthalein excretion, and thymol turbidity. In studies of 45 patients receiving corticotropin, Bernfeld and associates [18] noted a marked decrease in the beta globulin. A fall in blood bile acid in patients with cholangiolitic cirrhosis who received corticotropin was noted by Flink and Williams.[19] A marked fall in bilirubin in five patients with acute viral hepatitis who received corticotropin was reported by Colbert and associates.[20] They noted variable results in the thymol turbidity.

Biongiovanni and Eisenmenger [21] reported a slight decrease in serum bilirubin, gamma globulin, and increase in serum cholesterol esters, and variable changes in the thymol turbidity, serum albumin, and total cholesterol in patients with chronic liver disease receiving corticotropin. A decrease in serum bilirubin, a slight decrease in the thymol turbidity and gamma globulin, and a slight increase in both the cholesterol and the cholesterol esters was noted by Gyorgy and Bluemle.[22] Thorn [23] in 1953 stated that it is doubtful whether the course of liver disease is significantly altered by corticotropin.

METHODS

The present study was designed to determine the effect of stress or trauma upon the impaired liver and to compare it with the effect upon the normal liver.

In the first part of the study a course of corticotropin was chosen to simulate a type of "stress" which would be free of such complicating factors as anesthesia, blood loss, and tissue destruction. It is clear that such a selection is open to criticism and subject to pitfalls. It is hoped, however, that the effect of corticotropin (being in many respects similar to those of a bona fide "stress") would be of sufficient value to aid in the comparison of stress with anesthesia and without anesthesia. It is also clear that such a selection is almost one of necessity, since it is difficult to conceive of any other humane form of stress which might be used repeatedly in longterm studies on dogs.

In the second part of the study a standard operation under general anesthesia was selected to serve as stress.

The effect of both forms of "stress" have been studied, first, in the presence of normal liver function and, second, in the presence of impaired liver function due to chronic biliary obstruction.

A. Effect of Corticotropin.—The effect of corticotropin was studied first. Base line liver function studies were done in a series of six normal dogs. These consisted in determinations of serum total protein; albumin; globulin; nonprotein nitrogen[24]; free, esterified, and total cholesterol[25]; alkaline phosphatase[26]; direct and indirect bilirubin[27]; thymol turbidity,[28] and plasma prothrombin,[29] and the intravenous blood galactose tolerance test.*

1. Effect of Corticotropin on the Normal Liver: Each dog was then given a short, intensive five-day course of corticotropin. A total of 270 mg. of long-acting corticotropin gel† was given with 100 mg., 100 mg., 40 mg., 20 mg., and 10 mg. (in two equally divided doses at 12-hour intervals intramuscularly) on each of the five days. Blood eosinophile counts were performed daily to ensure efficacy of the material. The above-described liver function tests were repeated on the first, third, fifth, and tenth days following the start of the corticotropin.

2. Effect of Corticotropin on the Liver with Complete Biliary Obstruction: After a length of time varying from one to five days each dog was operated upon under intravenous pentobarbital (Nembutal) anesthesia. The common duct was divided and ligated to create complete biliary obstruction. A biopsy specimen of the liver was taken for microscopic examination. After the operation the liver function studies were repeated at intervals of a few days to follow the course of impairment.

Approximately six weeks after the operation, when liver function impairment was evident, a second course of corticotropin was given to each dog. The tests were then repeated, as before on the first, third, fifth, and tenth days following the start of the course.

* References 30, 31, 32, and 33.

† Acthar-gel, supplied by Armour Laboratories, Chicago.

B. Effect of Standard Operation.—The influence of a standard operation upon both the normal liver and the impaired liver was then studied.

1. Effect of Standard Operation on Normal Liver: Base line liver function tests were done on a series of seven normal dogs. A standard operation was then performed on each dog. This consisted of a laparotomy and liver biopsy under ether anesthesia in two dogs and of a laparotomy, small bowel division, and anastamosis and liver biopsy under intravenous pentobarbital anesthesia in five dogs. After operation the liver function tests were repeated on the first, third, fifth, and tenth days.

2. Effect of Standard Operation on Liver with Complete Biliary Obstruction: After a length of time varying from one to five days the dogs then underwent division and ligation of the common duct to produce a complete biliary obstruction. The liver function tests were then repeated at intervals to follow the course of impairment.

Six weeks later the dogs were given a second standard operation. The liver function tests were again repeated on the first, third, fifth, and tenth days.

RESULTS

The data are represented by Figures 1 to 5. To show the influence of both corticotropin and a standard operation upon the obstructed liver it has been necessary to rechart data previously reported [1] concerning the course of liver function following complete biliary obstruction. These results of detailed liver function studies in six dogs with complete biliary obstruction have been averaged and serve as a control for the present studies.

The minor changes noted in the present series are not statistically significant in view of the small number of dogs successfully surviving the long-term experiments. Average figures under such circumstances have little meaning unless the term "trend" can be applied. Since such data are expensive and tedious to obtain, since if the series were larger in number the changes noted might be significant, and since some of the changes noted confirm clinical observations,‡ these changes are described as trends. They are, however, minor in degree and are of only questionable significance.

‡ References 7 and 8.

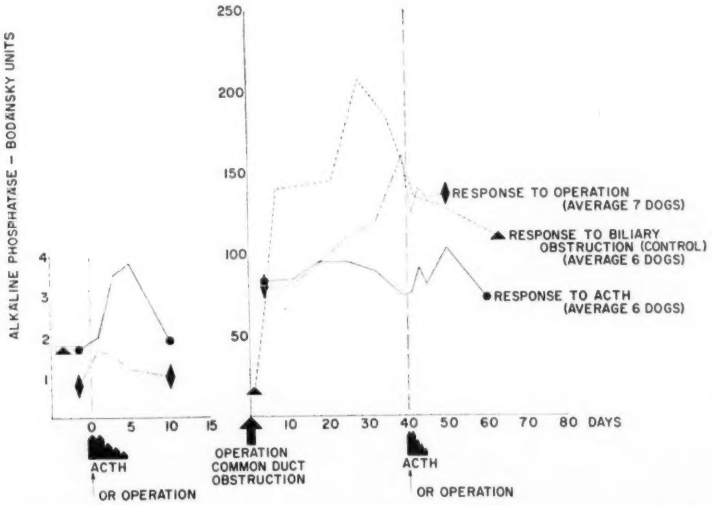


Fig. 1.—This graph and the following graphs show the changes observed in the liver function tests in two groups of dogs following either a standard operation or a standard course of corticotropin. The changes noted in normal dogs are shown in the graph on the left. The time interval between the two graphs varied from one to five days. The obstructive course of the liver function tests in these two groups of dogs are compared in the graph on the right with a third group of control dogs who received no corticotropin or standard operation following complete biliary obstruction. It will be noted that both the corticotropin and the standard operation are followed by a slight rise in the level of serum alkaline phosphatase in the presence of a normal liver and in the presence of chronic biliary obstruction.

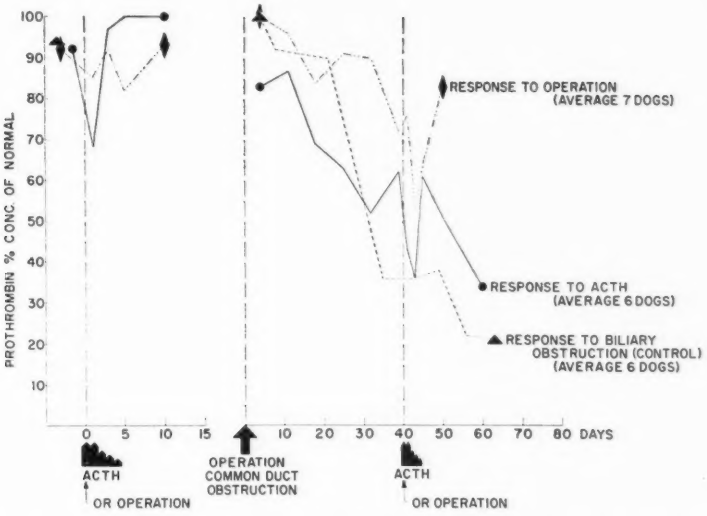


Fig. 2.—This graph shows a temporary depression of plasma prothrombin following both corticotropin and a standard operation in the presence of chronic biliary obstruction. A similar change occurred in the normal dog after only corticotropin.

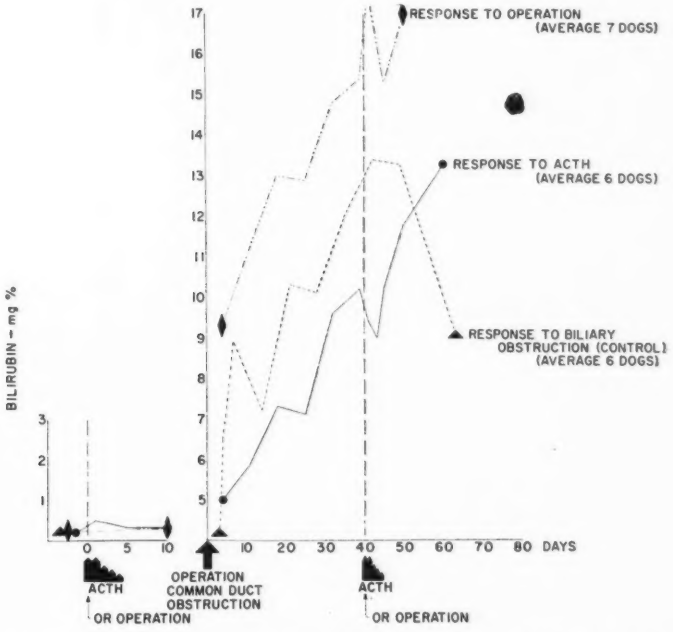


Fig. 3.—This graph shows a rise in serum bilirubin in the dogs with obstructive jaundice following both corticotropin and a standard operation, in contrast to the same dogs without obstruction and in contrast to the control group, which received no stress.

A. Serum Alkaline Phosphatase (Fig. 1).—Both corticotropin and the standard operation caused a slight rise in the level of serum alkaline phosphatase in the presence of a normal liver. This rise was also noted to a more marked degree in the presence of chronic biliary obstruction.

B. Plasma Prothrombin (Fig. 2).—Both corticotropin and the standard operation caused a temporary depression of the plasma prothrombin in the presence of chronic biliary obstruction. Whereas a similar change was produced by the corticotropin with normal liver function, our data showing the influence of the standard operation were inconclusive.

C. Serum Bilirubin (Fig. 3).—Neither corticotropin nor the standard operation caused a significant change in the level of serum bilirubin in the presence of normal liver function. However, both corticotropin

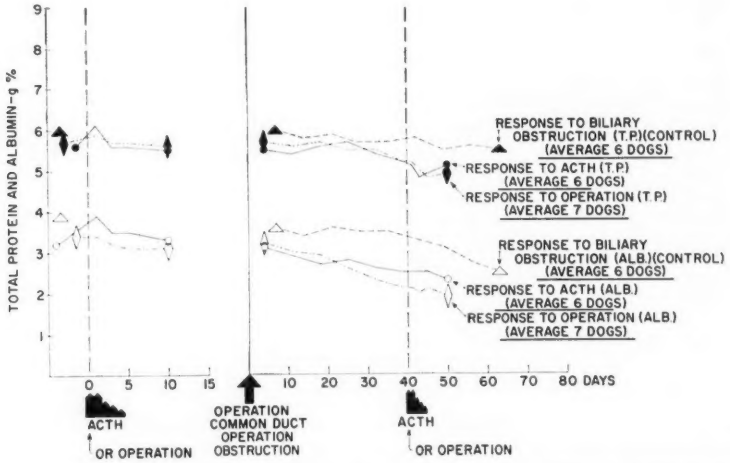

TOTAL PROTEIN AND ALBUMIN—g %
RESPONSE TO BILIARY OBSTRUCTION (T.P)(CONTROL) (AVERAGE 6 DOGS)
RESPONSE TO ACTH (T.P) (AVERAGE 6 DOGS)
RESPONSE TO OPERATION (T.P) (AVERAGE 7 DOGS)
RESPONSE TO BILIARY OBSTRUCTION (ALB.)(CONTROL) (AVERAGE 6 DOGS)
RESPONSE TO ACTH (ALB.) (AVERAGE 6 DOGS)
RESPONSE TO OPERATION (ALB.) (AVERAGE 7 DOGS)
80 DAYS
ACTH OR OPERATION
OPERATION COMMON DUCT OBSTRUCTION
ACTH OR OPERATION

Fig. 4.—This graph shows that neither the corticotropin nor the standard operation caused a significant change in the level of serum albumin or total protein in the presence of either a normal or an obstructed liver.

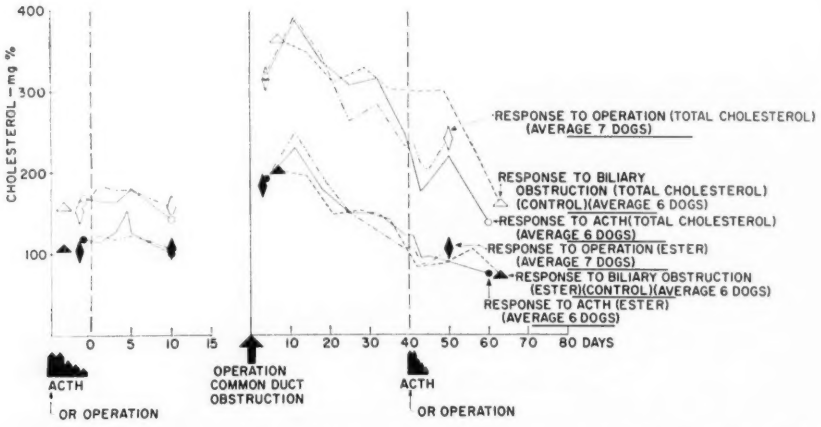

CHOLESTEROL—mg %
RESPONSE TO OPERATION (TOTAL CHOLESTEROL) (AVERAGE 7 DOGS)
RESPONSE TO BILIARY OBSTRUCTION (TOTAL CHOLESTEROL) (CONTROL)(AVERAGE 6 DOGS)
RESPONSE TO ACTH(TOTAL CHOLESTEROL) (AVERAGE 6 DOGS)
RESPONSE TO OPERATION (ESTER) (AVERAGE 7 DOGS)
RESPONSE TO BILIARY OBSTRUCTION (ESTER)(CONTROL)(AVERAGE 6 DOGS)
RESPONSE TO ACTH (ESTER) (AVERAGE 6 DOGS)
80 DAYS
ACTH OR OPERATION
OPERATION COMMON DUCT OBSTRUCTION
ACTH OR OPERATION

Fig. 5.—This graph shows that neither the corticotropin nor the standard operation caused a significant change in the level of serum cholesterol ester or total cholesterol in the presence of either a normal or an obstructed liver.

and the standard operation caused a delayed rise in the level of serum bilirubin in the presence of an obstructed liver. This rise is in sharp contrast to the gradual fall at this time in the control group described by several authors,§ and interpreted by Robscheit-Robbins and Whipple [37] as being due to to falling off in hemoglobin parent substances. It should further be noted in Figure 3 that the level of bilirubin in all dogs was normal immediately prior to common-duct ligation, although this is not shown on the graph. Thus the curves are similar in shape until immediately after the second stressing operation or course of corticotropin.

D. Serum Total Protein and Albumin (Fig. 4).—Neither corticotropin nor the standard operation caused a significant change in the level of serum albumin or total protein in the presence of either a normal or an obstructed liver.

E. Cholesterol Ester and Total Cholesterol (Fig. 5).—Neither corticotropin nor the standard operation caused a significant change in the level of serum cholesterol ester or total cholesterol in the presence of either a normal or an obstructed liver.

F. Serum Thymol Turbidity Test.—Neither corticotropin nor the standard operation caused a significant change in the serum thymol turbidity test in the presence of either a normal or an obstructed liver.

G. Intravenous Galactose Tolerance Test.—Neither corticotropin nor the standard operation caused a significant change in the galactose tolerance test in the presence of either a normal or an obstructed liver.

H. Liver Biopsy and Autopsy Results.—The liver specimens taken for biopsy prior to biliary obstruction revealed normal liver in all but one case. In this single instance there was evidence of minimal hepatitis in the biopsy specimen but only biliary cirrhosis present at autopsy. The autopsy examination, gross and microscopic, in all cases revealed biliary cirrhosis and complete biliary obstruction. In the majority of cases the kidneys showed varying degrees of cloudy tubular degeneration and pigmented casts.

§ References 34, 35, and 36.

COMMENT

The results of the present study indicate that, in general, the effects of stress upon liver function in the dog with obstructive jaundice are minor. The effects noted consist of a rise in serum bilirubin and alkaline phosphatase and a fall in plasma prothrombin. Some effects are also noted upon the normal liver but to a lower degree. These are a rise in serum alkaline phosphatase and a fall in plasma prothrombin. The difference between the effect upon the obstructed liver and that upon the normal liver was noted in only two tests. The others were essentially unchanged. These two were the serum alkaline phosphatase and the serum bilirubin.

Although alkaline phosphatase is found in many tissues throughout the body and although it is possible that the source of the rise observed in these dogs after stress might be elsewhere than the liver, it seems highly unlikely. The greater rise after stress in the dog with obstructive jaundice would be wholly unexpected if the source were the brain, the bone marrow, or the intestine, since it is difficult to see how biliary obstruction could make such a difference in the ability of such sources to respond. Thus, it is believed that the changes noted may reflect an influence of stress upon the ability of the liver to produce alkaline phosphatase.

It is also possible that the changes noted in the serum bilirubin in the dogs with obstructive jaundice might reflect a deleterious influence upon the extrahepatic excretion, such as renal or that through the wall of the colon. It is, however, unlikely that such an effect would depend upon the extrahepatic excretion, be unnoticed in the normal dog, and yet be so different in the dog with biliary obstruction. By similar reasoning it is unlikely that the rise noted could be due to a sudden increase in bilirubin production. It is also difficult to relate the changes observed to liver excretion in view of the complete obstruction. Therefore, at the present time these changes cannot be explained.

The effects described are observed when either a standard operation or a course of corticotropin is used as the stress mediator. Furthermore, the degree of effect in these two instances is of the same order of magnitude. Thus the anesthetic agents used (pentobarbital and ether) did not have a significant additive effect in these experiments. This would substantiate the clinical impression of French and associates[8] that the changes in liver function noted in man following operation under anesthesia were due to the nonspecific stress of the operation rather than the anesthetic.

It is noteworthy that neither form of "stress" produced a significant deleterious effect in spite of impaired liver function. The validity of comparison of these observations in the dog with those in the human is, of course, questionable. However, a gross comparison seems justified and is supported by clinical experience.‖

SUMMARY

The influence of two types of experimental "stress" upon the normal liver and upon the liver in obstructive jaundice has been studied in dogs by surveying multiple liver functions.

In general, the effects noted were not statistically significant.

The normal liver showed function changes minor in degree and temporary in duration, consisting of only (*a*) a rise in serum alkaline phosphatase and (*b*) a fall in plasma prothrombin.

The obstructed liver showed function changes consisting of (*a*) a rise in serum bilirubin, (*b*) a rise in serum alkaline phosphatase, and (*c*) a fall in plasma prothrombin.

A difference between the effect of stress on the normal and on the obstructed liver was noted in only two tests. These were the serum alkaline phosphatase and the serum bilirubin tests. These changes are of questionable significance.

The anesthetic agents used (pentobarbital and ether) had no apparent effect upon these results.

Under the conditions of this experiment, the presence of chronic biliary obstruction did not significantly alter the animals' response to "stress" in terms of liver function.

Mrs. Anna Marie Lowe and Miss Mary Louise Willcox provided technical assistance in this study.

REFERENCES

1. Macgregor, C. A.: Nature of Liver Failure Due to Complete Biliary Obstruction, A. M. A. Arch. Surg. **67**:878 (Dec.) 1953.

2. Fine, J.; Seligman, A. M., and Frank, H. A.: Specific Role of the Liver in Hemorrhagic Shock: Report of Progress to Date, Ann. Surg. **126**:1002 (Dec.) 1947.

3. Moon, V. H.: The Pathology of Secondary Shock, Am. J. Path. **24**:235 (March) 1948.

4. Levin, L.: Physical Stress and Liver Fat Content of the Fasted Mouse, Federation Proc. **8**:218 (March) 1949.

5. Gillman, J., and Gillman, T.: Anoxia and the Liver with Special Reference to Shock and Chronic Malnutrition, Am. J. Digest. Dis. **16**:348 (Oct.) 1949.

6. Frank, H. A.: Present Day Concepts of Shock, New England J. Med. **249**:445 (Sept. 10) 1953.

7. Fairlie, C. W.; Barss, T. P.; French, A. B.; Jones, C. M., and Beecher, H. K.: Metabolic Effects of Anesthesia in Man: IV. A Comparison of the Effects of Certain Anesthetic Agents on the Normal Liver, New England J. Med. **244**:615 (April 26) 1951.

8. French, A. B.; Barss, T. P.; Fairlie, C. B.; Bengle, A. L., Jr.; Jones, C. M.; Linton, R. R., and Beecher, H. K.: Metabolic Effects of Anesthesia in Man: V. A Comparison of the Effects of Ether and Cyclopropane Anesthesia on the Abnormal Liver, Ann. Surg. **135**:145 (Feb.) 1952.

9. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15 (Jan.) 1948.

10. Sayers, G.; Burns, T. W.; Tyler, F. H.; Jager, B. V.; Schwartz, T. B.; Smith, E. L.; Samuels, L. T., and Davenport, H. W.: Metabolic Actions and Fate of Intravenously Administered Adrenocorticotropic Hormone in Man, J. Clin. Endocrinol. **1**:593 (July) 1949.

11. Thorn, G. W., and Forsham, P. H.: Metabolic Changes in Man Following Adrenal and Pituitary Hormone Administration in Pincus, G., Editor: Recent Progress in Hormone Research: Proceedings of the Laurentian Hormone Conference, New York, Academic Press, Inc., 1949, Vol. 4, Pt. 2, pp. 229.

‖ References 7 and 8.

12. Adlersberg, D.; Schaefer, L. E., and Drachman, S. R.: Development of Hypercholesteremia During Cortisone and ACTH Therapy, J. A. M. A. **144**:909 (Nov. 11) 1950.

13. Sprague, R. G.; Power, M. H., and Mason, H. L.: Physiological Effects of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) in Man, J. A. M. A. **144**:1341 (Dec. 16) 1950.

14. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950.

15. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum Cholesterol: A Probable Precursor of Adrenal Cortical Hormone, J. Lab. & Clin. Med. **35**:504 (April) 1950.

16. Thorn, G. W., and others: Medical Progress: Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:824 (May 25) 1950.

17. Havens, W. P., Jr.; Myerson, R. M., and Carroll, I. N.: Effect of ACTH, Cortisone and Progesterone on Patients with Chronic Hepatic Disease, Metabolism **1**:172 (March) 1952.

18. Bernfeld, P.; Bonner, C. D., and Homburger, F.: ACTH and Plasma Proteins, in Mote, J. R., Editor: Proceedings of Second Clinical ACTH Conference, New York, The Blakiston Company, 1951, Vol. 1, p. 282.

19. Flink, E. B., and Williams, C. F.: The Treatment of Chronic Liver Disease with Pituitary Adrenocorticotropic Hormone (ACTH), J. Lab. & Clin. Med. **36**:822 (Nov.) 1950.

20. Colbert, J. W., Jr.; Holland, J. P.; Heissler, L., and Knowlton, M.: The Use of ACTH in Acute Viral Hepatitis, in Mote, J. R., Editor: Proceedings of Second Clinical ACTH Conference, New York, The Blakiston Company, 1951, Vol. 1, p. 371.

21. Bongiovanni, A. M., and Eisenmenger, W. J.: Observations During the Administration of ACTH to Patients with Chronic Liver Disease, in Mote, J. R., Editor: Proceedings of Second Clinical ACTH Conference, New York, The Blakiston Company, 1951, Vol. 1, p. 390.

22. Gyorgy, P., and Bluemle, L. W., Jr.: The Treatment of Chronic Inflammatory Liver Disease with ACTH and Cortisone, in Mote, J. R., Editor: Proceedings of Second Clinical ACTH Conference, New York, The Blakiston Company, 1951, Vol. 1, p. 386.

23. Thorn, G. W.; Jenkins, D.; Laidlaw, J. C.; Gortz, F. C.; Dingiman, J. F.; Arons, W. L.; Streeten, D. H. P., and McCracken, B. H.: Pharmacologic Aspects of Adrenocortical Steroids in Man, New England J. Med. **248**:369 (April 2) 1954.

24. Peters, J. P., and Van Slyke, D. D.: Determinations of Plasma Nitrogen, in Quantitative Clinical Chemistry, Vol. II, Methods, Baltimore, Williams & Wilkins, Company, 1932, pp. 291-393.

25. Sperry, W. M., and Webb, M. A.: A Revision of the Schoenheimer-Sperry Method for Cholesterol Determination, J. Biol. Chem. **187**:97 (Nov.) 1950.

26. Bodansky, A.: Notes on Determination of Serum Inorganic Phosphate and Serum Phosphatase Activity, Am. J. Clin. Path. (Tech. Supp.) **7**:51 (Sept.) 1937.

27. Malloy, H. T., and Evelyn, K. A.: Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

28. Ducci, H.: Thymol Test of Maclagen: Standardization and Adaptation to Evelyn Photoelectric Colorimeter, J. Lab. & Clin. Med. **32**:1266 (Oct.) 1947.

29. Aggeler, P. M.; Howard, J.; Lucia, S. P.; Clark, W., and Astoff, A.: Standardization of the Quick Prothrombin Test, Blood, **1**:220 (May) 1946.

30. King, E. J., and Aiken, R. S.: An Intravenous Galactose-Tolerance Test, Lancet **2**:543 (Nov. 2) 1940.

31. Colcher, H.; Patek, A. J., Jr., and Kendall, F. E.: Galactose Disappearance from the Blood Stream: Calculation of Galactose Removal Constant and Its Application as a Test for Liver Function, J. Clin. Invest. **25**:768 (Sept.) 1946.

32. Raymond, A. L., and Blanco, J. G.: Blood Sugar Determination and Separation of Sugars with Live Yeast, J. Biol. Chem. **79**:649 (Oct.) 1928.

33. Benedict, S. R.: The Determination of Blood Sugar II, J. Biol. Chem. **76**:457 (Feb.) 1928.

34. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:471 (Oct.) 1927.

35. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of Blood and Their Relation to Coagulation, Arch. Surg. **29**:277 (Aug.) 1934.

36. Tanturi, C. A.; Canepa, J. F.; Bay, R., and Banfe, R. F.: Experimental Study on Liver Function Tests, Surg., Gynec. & Obst. **83**:171 (Aug.) 1946.

37. Robscheit-Robbins, F. S., and Whipple, C. H.: Hemoglobin Production Factors in the Human Liver: II. Liver Degeneration, Cancer, Cirrhosis and Hepatic Insufficiency, J. Exper. Med. **57**:653 (April) 1933.

A Bacteriologic Study of Portal-Vein Blood in Man

WILLIAM E. SCHATTEN, M.D.
JOHN D. DESPREZ, M.D.
and
WILLIAM D. HOLDEN, M.D., Cleveland

Previous studies have been done in this laboratory to ascertain the role of intestinal bacteria in hepatic necrosis following excision of the hepatic arterial vasculature in dogs.[1] It was demonstrated by culturing portal-vein blood from apparently normal healthy dogs that there was continual seeding of the liver by bacteria that passed from the gastrointestinal tract to the liver by way of the portal vein. It has not been shown in man that bacteria migrate from the gastrointestinal tract into the portal circulation, except in the presence of serious intraperitoneal infections or inflammatory lesions of the gastrointestinal tract. This investigation was undertaken in order to determine whether bacteria enter the portal circulation in the absence of infectious processes.

MATERIALS AND METHODS

Portal-vein blood obtained from 25 patients at the time of laparotomy was cultured. There was no selection of patients with regard to intraabdominal pathology or type of operation, except that specimens were not obtained from patients with inflammatory lesions of the gastrointestinal tract. In all instances portal-vein blood was obtained before the gastrointestinal or biliary tract was opened. Portal-vein blood was obtained at varying intervals of time after the peritoneal cavity was entered, depending upon the type of operation and the technical facility with which the portal vein could be exposed. In three patients blood was obtained for culture shortly after the peritoneal cavity was opened and again at the termination of the operative procedure, just before the abdominal wall was closed. Blood was obtained from the portal vein by aspiration through a 20-gauge needle. A small amount of sterile heparin was aspirated through the needle just before the needle and syringe were used to obtain a sample of blood. Ten to fifteen milliliters of blood was aspirated and immediately placed in a sterile bottle. In all but three patients a sample of blood was obtained for culture concomitantly from an arm vein. Each blood sample was cultured aerobically and anaerobically in tryptose broth * and Brewer thioglycollate medium.† The heparin used to prevent coagulation was cultured separately each time.

RESULTS

A summary of the bacteriologic studies of portal-vein blood of the patients included in this report is shown in the Table. It can be seen that two samples of portal-vein blood were obtained from the first three patients who are listed in the table. Organisms were cultured from the portal-vein blood of eight patients. It is interesting that Gram-positive cocci were isolated in six of these positive portal-vein cultures. As would be expected because of the location of the portal vein, the majority of the patients from whom samples were obtained had biliary tract disease. However, it is believed that there was no relationship between the dis-

Received for publication April 25, 1955.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

Department of Surgery, Western Reserve University School of Medicine and University Hospitals of Cleveland.

Support by Medical Research and Development Board, Department of the Army. Grant # DA-49-007-MD-520.

* Made by Digestive Ferments Company.

† Made by Baltimore Biological Laboratories.

Bacteriologic Studies of Portal Vein Blood

Patient	Age	Diagnosis, Operation	Preoperative Antibiotic Therapy	Portal Vein Culture	Peripheral Vein Culture
M. W.	50	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth (early sample) No growth (late sample)	....
W. K.	35	Chronic recurrent pancreatitis Sphincterotomy	None	No growth (early sample) No growth (late sample)	No growth No growth
M. S.	30	Acute and chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth (early sample) Staphylococcus albus (late sample)	No growth No growth
D. R.	53	Sarcoma of stomach Gastric resection	None	Escherichia coli	.....
A. C.	43	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	Staphylococcus albus	No growth
G. H.	61	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	Clostridium welchii	No growth
P. H.	21	Acute and chronic cholecystitis and cholelithiasis Cholecystectomy	None	Staphylococcus albus	No growth
E. L.	57	Chronic pancreatitis Exploration of biliary tract	None	Streptococcus viridans, yeasts	No growth
E. S.	46	Acute and chronic cholecystitis and cholelithiasis Cholecystectomy, Choledocholithotomy	300,000 v APP * q12h × 7 days	Streptococcus viridans Neisseria catarrhalis	No growth
J. K.	78	Chronic cholecystitis and cholelithiasis Cholecystectomy	300,000 v APP and 0.5 gm. Streptomycin q12h × 10 days	Staphylococcus albus	No growth
L. Y.	55	Chronic cholecystitis and cholelithiasis Cholecystectomy	300,000 v APP q12h × 7 days 0.25 gm. Terramycin q6h × 5 days	No growth	No growth
W. W.	40	Acute and chronic cholecystitis and cholelithiasis Cholecystectomy	300,000 v APP q12h × 6 days	No growth	No growth
M. T.	76	Gastric ulcer Gastric resection	None	No growth	No growth
S. W.	42	Gastric ulcer Gastric resection	None	No growth	.....
A. W.	44	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth	No growth
B. M.	43	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth	No growth
S. S.	55	Acute and chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth	No growth
M. M.	50	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth	No growth
E. Y.	72	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	No growth	No growth
E. P.	27	Acute and chronic cholecystitis Cholecystectomy	None	No growth	No growth
J. E.	64	Duodenal ulcer Gastric resection	None	No growth	No growth
C. G.	47	Duodenal ulcer Gastric resection	None	No growth	No growth
M. O.	66	Exploratory laparotomy	None	No growth	No growth
S. G.	45	Chronic cholecystitis and cholelithiasis Cholecystectomy	None	.....	No growth
M. L.	65	Gastric ulcer Gastric resection	None	.....	No growth

* APP, aqueous procaine penicillin G.

ease process and the presence of organisms in portal-vein blood, because samples were obtained for culture before the biliary tract was opened. It can be seen in the Table that four of the patients in this series received antibiotics for 5 to 10 days preoperatively. Two of these four patients had positive portal-vein cultures. Cultures of peripheral vein blood were not positive in any instances.

COMMENT

The results of this study demonstrate that bacteria pass from the gastrointestinal tract to the liver by way of the portal vein. This

was evidenced by positive cultures of portal-vein blood in 32% of patients undergoing laparotomy and in negative cultures of peripheral vein blood obtained concomitantly. The predominance of Gram-positive cocci in these cultures is in keeping with findings in a previous study by one of us (W. E. S.) of the bacteria in portal-vein blood in dogs.[1] The reason Gram-positive cocci pass the gastrointestinal barrier in greater numbers than Gram-positive or Gram-negative bacilli is not known.

There was no correlation between the extent of dissection and amount of operative time necessary to obtain portal-vein blood with the presence of organisms in the blood sample. Negative cultures occurred in many patients in whom exposure of the portal vein was the most difficult, and positive cultures occurred in many patients in whom little dissection was necessary before a blood sample was obtained. There was also no correlation between the acuteness or chronicity of the disease process for which the patient was operated on and the presence of organisms in portal-vein blood. It is believed that the results of this study show that there is continual passage of bacteria from the gastrointestinal tract to the liver through the portal vein and that the positive blood cultures were not the direct result of operative manipulation or the underlying disease. The three patients from whom samples were obtained for culture shortly after the peritoneal cavity was entered and again just before the peritoneum was closed comprise a small group, but a positive culture following a previous negative one occurred in only one instance.

The finding of positive cultures in two of the four patients who had large quantities of antibiotics preoperatively is in keeping with the facts that these bacteria come from the gastrointestinal tract and parenteral administration of pencillin and streptomycin do not effect sterilization of that system. It was shown in a previous study that positive portal-vein blood cultures were obtained in 60% of apparently healthy nontreated dogs, but no positive cultures were obtained in dogs in which the gastrointestinal tract had previously been sterilized with orally administered neomycin.[1]

It has been shown by Beeson, Brannon, and Warren that the liver is an excellent filtering mechanism and that bacteria are removed from the blood stream principally by that organ.[2] The marked phagocytic capacity of the unimpaired liver is further demonstrated by the findings of this study that there is continual seeding of the liver by intestinal bacteria. Several workers have shown previously that cultures of normal human liver are negative.‡

This finding of continual passage of intestinal bacteria to the liver in man is an explanation of the reason antibiotics have been found to be of definite value after hepatic artery ligation § and in the treatment of acute and chronic diseases in which there is severe hepatic insufficiency.|| This process of continual bacterial seeding of the liver explains the many cases reported prior to the widespread use of antibiotics in which hepatic artery ligation in man was followed by liver necrosis and subsequent death.¶ Since hepatic tissue cultures in man show there is no endogenous liver flora and it has been shown experimentally that sterilization of the gastrointestinal tract with a nonabsorable antibiotic affords protection to the liver after complete excision of the hepatic arterial vasculature, the portal vein must be the route of entry and intestinal bacteria must be responsible for hepatic infection in the presence of ischemia. The fact that changes are usually severer in the left lobe of the liver in cases of acute hepatic necrosis [8] is especially interesting because there is a selective distribution of portal blood in the liver and the left lobe receives blood from the colon, the site of greatest bacterial growth.#

Whipple and Harris have reported the frequency of bacteremia in patients who have advanced cirrhosis.[15] On the basis of those

‡ References 3 and 4.

§ References 5, 6, and 7.

|| References 8 and 9.

¶ References 10, 11, and 12.

References 13 and 14.

observations, these workers and others [16] have postulated that at times the portal circulation contains organisms entering from the intestinal walls, but this has not been shown previously.

The demonstrating of passage of bacteria from the intestinal tract to the liver by way of the portal vein provides a basis for sterilizing the gastrointestinal tract of all patients who have a serious reduction in liver function.

CONCLUSIONS

1. There is continual seeding of the liver by bacteria that pass from the gastrointestinal tract to the liver by way of the portal vein.

2. Gram-positive cocci are cultured more frequently from portal-vein blood than are other organisms.

3. There is rationale for sterilizing the gastrointestinal tract in all instances in which there is a significant degree of impairment of hepatic function.

REFERENCES

1. Schatten, W. E.: The Role of Intestinal Bacteria in Liver Necrosis Following Experimental Excision of the Hepatic Arterial Supply, Surgery **36**:256, 1954.

2. Beeson, P. B.: Brannon, E. S., and Warren, J. V.: Observations on Sites of Removal of Bacteria from Blood in Patients with Bacterial Endocarditis, J. Exp. Med. **81**:9, 1945.

3. Romieu, C., and Brunschwig, A.: Bacteriologic Study of the Human Liver, Surgery **30**:621, 1951.

4. Sborov, V. M.; Morse, W. C.; Giges, B., and Jahnke, E. J., Jr.: Bacteriology of the Human Liver, J. Clin. Invest. **31**:986, 1952.

5. Berman, J. K., and Hull, J. E.: Hepatic, Splenic, and Left Gastric Arterial Ligations in Advanced Portal Cirrhosis, A. M. A. Arch. Surg. **65**:37, 1952.

6. Rienhoff, W. F., Jr.: Ligation of the Hepatic and Splenic Arteries in Treatment of Portal Hypertension with Report of Six Cases, Bull. Johns Hopkins Hosp. **88**:368, 1951.

7. Smith, J. C.; McNealy, R. W., and Zaus, E. A.: Effect of Hepatic Artery Ligation on Ascites Due to Laennec Cirrhosis, A. M. A. Arch. Surg. **66**:344, 1953.

8. Farquhar, J. D.; Stokes, J., Jr.; Whitlock, C. M., Jr.; Bluemle, L. W., Jr., and Gambescia, J. M.: Studies on the Use of Aureomycin in Hepatic Disease; Note on Aureomycin Therapy in Hepatic Coma, Am. J. M. Sci. **220**:166, 1950.

9. Goldbloom, R. S., and Steigmann, F.: Aureomycin Therapy in Hepatic Insufficiency, Gastroenterology **18**:93, 1951.

10. Behrend, M.: Experimental Ligation of Hepatic Artery, Surg. Gynec. & Obst. **31**:182, 1920.

11. Friedenwald, J., and Tannenbaum, K. H.: Aneurysm of Hepatic Artery, Am. J. M. Sc. **165**: 11, 1923.

12. Holst, S. F.: Ligation of Hepatic Artery, Norsk Mag. f. Lægvidensk **81**:1182, 1920; quoted by Segall, M. N.: Experimental Anatomical Investigation of Blood and Bile Channels of the Liver, Surg. Gynec. & Obst. **37**:152, 1923.

13. Copher, G. H., and Dick, B. M.: "Streamline" Phenomena in Portal Vein and Selective Distribution of Portal Blood in Liver, Arch. Surg. **17**:408, 1928.

14. Hahn, P. F.; Donald, W. D., and Grier, R. C., Jr.: Physiological Bilaterality of the Portal Circulation; Streamline Flow of Blood into Liver as Shown by Radioactive Phosphorus, Am. J. Physiol. **143**:105, 1945.

15. Whipple, R. L., Jr., and Harris, J. F.: B. Coli Septicemia in Laennec's Cirrhosis of the Liver, Ann. Int. Med. **33**:462, 1950.

16. Boyd, W.: A Textbook of Pathology; An Introduction to Medicine, Ed. 2, Philadelphia, Lea & Febiger, 1934.

DISCUSSION

On Papers by Drs. Macgregor, Griffith, and Munro and Schatten, Desprez, and Holden

Dr. Robert Watman, Columbus, Ohio: I should like to discuss Dr. Macgregor's paper and to thank him for this opportunity.

I think our knowledge of adrenocortical function and stress phenomena is still at the stage where we describe rather than explain. Some of the findings that Dr. Macgregor has described today are most provocative. They encourage speculation.

First, as the authors have been careful to point out, the similarity between stress phenomena and corticotropin administration cannot be assumed. It is well known that steroids of removed adrenals show many of the reactions to stress of the intact animal, and that while the steroids of the adrenal cortex are probably necessary to the stress phenomena they do not regulate the phenomena and perhaps do not initiate many of them.

In the present study there were some differences, mostly quantitative, between the effects of corticotropin administration and the effects of the nonspecific stress.

The changes in the serum alkaline phosphatase are interesting, but I think it is justifiable to ask, and I think Dr. Macgregor feels so also, how specifically this is referable to liver function. The response is known to occur in regenerating tissues that are actively synthesizing protein.

Observation on the serum bilirubin is remarkable itself. The falling bilirubin that is seen in the control animals with ligated bile ducts of four weeks suggests two possibilities, (1) that there is decreased production of bilirubin for some reason or (2) that perhaps there is a new or accelerated route of excretion of bilirubin at this time, so that the relative rise after corticotropin administration or after stress then must mean that there is either an improved synthesis of bilirubin or some interference with this new or accelerated route of excretion. I think that is most interesting.

The failure of the cholesterol to rise in the animals came to me as something of a surprise. A few years ago we made a study of the effects of cortisone on the chloroform-damaged liver in the rabbit, and in the presence of this liver damage instituted by chloroform administration, cortisone gave a marked hyperlipemia and a marked fatty infiltration of the liver as compared with the controls.

This elevation in the fat of the blood and of the liver affected mainly the cholesterol and the neutral fat fractions. In the present study there was no such rise, and I wonder whether the biliary exclusion and impaired fat digestion might not be involved in the difference between these observations on the chloroform-damaged liver and the study of the liver damaged by duct obstruction. It might be interesting, in that connection, to see what the effect of the feeding of bile to these duct-ligated animals might be on the cholesterol.

I think the authors are to be congratulated on a very nice study, one that has been scrupulously reported and scrupulously interpreted.

DR. WILLIAM A. ALTEMEIER, Cincinnati: Dr. Holden asked me to discuss the paper by Dr. Schatten. I am very pleased to do so.

In disease, of course, it has been very well known that septic embolization and thrombosis of the portal vein may occur from infections in various areas of the intestinal tract, such as gangrenous appendicitis, regional enteritis, or even ulcerated hemorrhoids. This sequence is the basis of the pathogenesis of liver abscess and of thrombophlebitis of the portal vein.

However, in health, no one has previously reported data to prove that bacteria migrate from the intestine to the liver through the portal vein. This concept has been held by various people but never has been proved.

Dr. Meleney, in one of his books, entitled "Treatise of Surgical Infections," assumes that this occurs but again states that it has never been proved.

The paper which we have heard today, therefore, is one of considerable significance in that it gives concrete evidence of this migration.

In 1938-1939, the late Roy D. McClure interested me in culturing portal blood removed by aspiration at the operating table during cholecystectomy. I have tried to locate these data but have been unable to do so. I was discouraged from reporting the data at that time by Dr. Hartman, Director of the laboratories at Ford Hospital, inasmuch as he believed that these positive cultures which we obtained were the result of contamination, probably from the lymphatics in the region of the common duct and the portal vein.

My recollection is that we obtained positive cultures in about one-fourth of the cases which we studied, but a variety of bacteria were found. Included most commonly in the varieties were the Streptococcus faecalis, which is at slight variance with the studies reported today. Other organisms were the Gram-negative intestinal organisms, diphtheroids and Clostidium welchii. In some instances we found two types simultaneously.

The significance of this excellent paper by Dr. Schatten and his co-workers is not entirely academic. Clinical importance of their results now and in the future may be given as follows:

1. Emphasis of the value of antibiotic prophylaxis in hepatic and splenic arterial ligations.

2. Suggestive evidence of the role of intestinal bacteria and their products in severe or irreversible shock. As you know, Fine, in Boston, has suggested that this is an important factor, and Culbertson, in my laboratory, is studying this aspect at the present time.

3. Possible explanation of the spontaneous bacteremia that develops in patients subjected to sublethal or lethal irradiation either by x-ray or by atomic irradiation to the entire body. In such instances, in our laboratory and elsewhere, nonspecific septicemia has been found within 12 hours of such irradiation and irregularly thereafter during the next 7 to 10 days.

4. Septicemia may be associated irregularly with cases of cirrhosis of the liver. In four of the cases we will report tomorrow, positive cultures were obtained from liver biopsies. Although Brunschwig and DeBakey have found that cultures of biopsies in the normal liver were negative, we feel that this is compatible with the results presented by Dr. Schatten, in that the organisms have been or can be removed by the normal liver through its effective reticulo-endothelial system.

The work presented today is highly significant and very interesting.

DR. C. A. MACGREGOR, Denver: As I mentioned in my introduction, our laboratory has been concerned with trying to pinpoint some of the important causes not only as to type but as to degree in patients who are jaundiced and who die after surgery.

Dr. Watman has asked three very pertinent questions in regard to our data. The first concerned the alkaline phosphatase. The other results which we have seen truly are a reflection of liver function. It would seem that, in spite of the fact that we know that alkaline phosphatase is present in many tissues throughout the body and in many systems, the difference between the response seen here in the normal dog, which was a very minor, almost insignificant response, in contrast with the response seen in the dog with the failing liver, and in contrast with the usual course of the alkaline phosphatase, I believe, probably justifies us in thinking of this as a change dependent upon liver function.

The same holds true with regard to the bilirubin. There was no significant effect at all in the level of the bilirubin in response to these two stress mediators in the normal dog, whereas in the dog with liver failure and an elevated bilirubin there was a rather definite rise.

This, then, probably relates to the insult or to the effect upon the ability of the liver cell and reticuloendothelial system to excrete the bilirubin, which is then picked up and excreted through the kidney.

I don't believe that we would see an effect of this type if the change were due to the ability of the kidney, for example, to excrete the bilirubin. Again, I believe, this is probably a reflection of trauma to the liver.

With regard to the cholesterol, I cannot answer the question. I leave it as an observation. Perhaps it is the difference between the rabbit and the dog.

The net effect of this material and the experiments which we have presented today is that, in spite of the fact that these dogs were near the end of their downward course due to biliary obstruction, there was really very little effect upon the liver function pattern as we can determine it as a whole.

I think this, then, points the finger in a different direction as to the cause of some of our deaths following surgery on jaundiced patients.

The Hazards of Surgery in Irradiated Tissue

DAVID W. ROBINSON, M.D., Kansas City, Kan.

Tissues subjected to irradiation undergo structural and physiologic changes often inexorably progressive. Surgical procedures may be performed in such tissues with good wound healing but also may be followed by serious complications which cause poor end-results, prolong hospitalization, and threaten life. Some of the complications that make surgery in irradiated tissue more difficult or hazardous are the following: (1) infection; (2) poor wound healing; (3) slough; (4) exposure of tendons, bone, or other important structures; (5) difficult hemostasis and/or secondary hemorrhage; (6) difficult dissections; (7) rapid spread of carcinoma released from the incarceration of fibrosis; (8) radio-osteonecrosis; (9) induced tissue allergies; (10) narcotic addition from treatment for intolerable pain, and (11) general inanition. All these are fundamentally the result of diminished blood supply, lowered vitality of the irradiated tissue, and excessive fibrosis.

Most all of these complications can and do follow surgery in normal tissues or in tissues damaged by causes other than irradiation. Surgery and irradiation are both destructive processes. The use of either method of treatment in combination with other forms of therapy, although improving the destructive action against the condition treated, adds considerably to the incidence of complications. The awareness of the frequency of these difficulties alters the surgeon's judgment in planning and performing operations in such tissue.

The pathogenesis of acute radiation changes has been well described,[1] and the dangers of too early surgery before necrosis is delimited are well known.* The late changes so ably first pointed out by Wolbach have been recently reemphasized.[5] Frequent repeated small doses of soft x-rays given for treatment of skin lesions and repeated x-ray or fluoroscopic exposure many years before usually cause the progressive changes of radiodermatitis. The massive treatment doses of harder rays, given to treat a disease at some depth in the body may not change the skin so profoundly but may produce deep changes. The pathognomonic signs of radiodermatitis are (1) patchy sclerosis and atrophy of skin that is dry, shiny, scaly, and hairless; (2) thin telangiectases and brown pigmented spots or black "coal spots"; (3) papillomatoses and keratoses and, later, frank epitheliomas, and (4) ulcers with dirty bases. Brown, dense, board-like, or armor-plate tissue adherent to and immobile over deeper structures indicates atrophy, fibrosis, and avascularity that follow some time after deeper destruction.

1. INFECTION

Infection is a very real danger. Many pathogenic bacteria may inhabit a radiation ulcer. The body's natural defenses to control such infection are diminished. The skin does not cleanse itself in the normal manner,† and mechanical cleansing is difficult, owing to the intense pain in these ulcers. No strong soaps, detergents, or chemicals should be used but, instead, gentle cleansing, often open sur-

Received for publication April 25, 1955.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Department of Surgery, Section of Plastic Surgery, University of Kansas Medical Center, Kansas City, Kan.

* References 2, 3, and 4.

† References 3 and 6.

Fig. 1 (Case 1).—A, plantar defect after repeated irradiation of

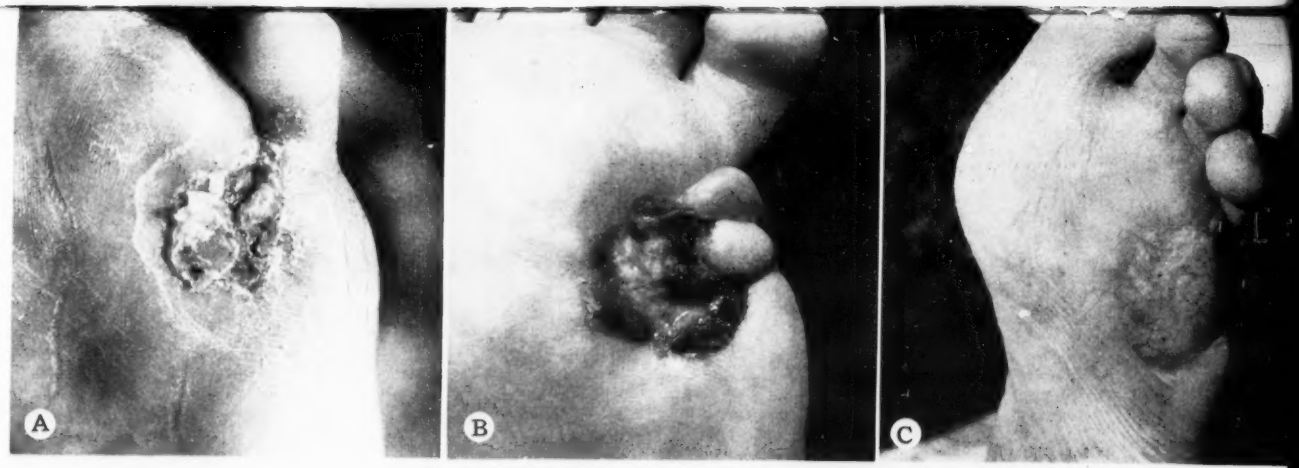


Fig. 1 (Case 1).—*A*, plantar defect after repeated irradiation of a wart in a 20-year-old youth. Crippling pain a prominent symptom. *B*, the necrotic flap of filleted small toe with apparent good blood supply three weeks later. Infection and poor minute blood supply in area are the cause of the slough. *C*, flap coverage by cross leg pedicle from calf finally gives good coverage but denies full use for several months.

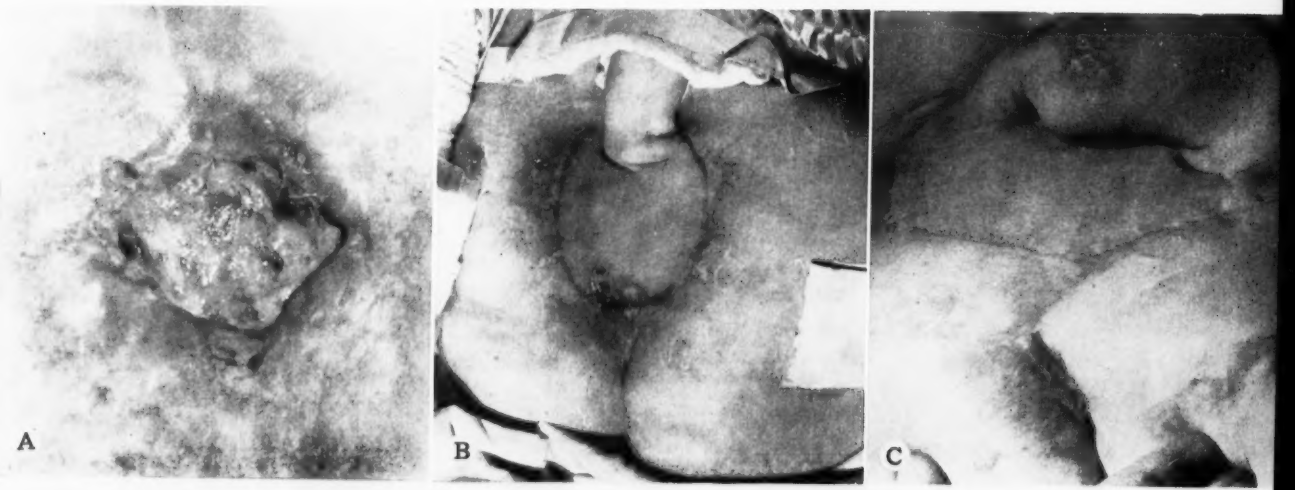


Fig. 2 (Case 2).—*A*, irradiation ulcer over sacrum of a 38-year-old woman, the result of treatment of a hemangioma a few years before. *B*, nearly complete coverage by four operations; two of these were partial sections of abdominal pedicle. Still small painful ulceration at lower end of pedicle. Note that pedicle is not large enough to cover all of pigmented irradiated area. *C*, bilateral rotation flaps from buttocks produced a serious wound infection with more slough. Later combination of use of rotation flaps and a portion of remaining bipedicled tube closed the defect finally, a little over one year after beginning the closure. Fingers are spreading gluteal cleft. Part of "suitcase handle" remains.

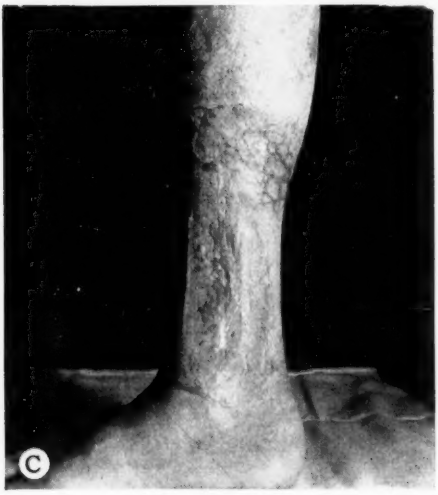


Fig. 3 (Case 3).—*A*, necrotic base of ulcer, the result of prolonged irradiation therapy given senselessly (not by an M.D.) to an acute thermal burn incurred several months before shown here. *B*, clean granulating base after débridement and deep excision, including cortex of tibia. *C*, good coverage with split-skin graft early. This has not stayed entirely healed. At present, there is an ulcer over bone 4×0.5 cm. directly over tibia.

gical drainage by frequent changes of wet dressings, and antibiotics to which the harbored organisms have proved sensitive. If surface healing, even though it may take a few weeks, can be accomplished conservatively, it should be complete before surgery.

2. WOUND HEALING

At surgery, tissue should be cut back to good bleeding beyond the areas of fibrosis. The required extent of excision is not easy to ascertain.[7] If much surface coverage is removed, simple closure is rarely possible because of poor blood supply and inflexibility of the wound sides. Wound coverage should be accomplished by the easiest means to insure healing. A thin split-skin graft can usually accomplish this, but a pedicle graft may be required if the blood supply is poor, if a free graft would likely fail, or if vital structures are exposed. A large pedicle flap should be planned[8] and perhaps elevated and/or delayed before its transfer. Early wound drainage for a day or two may obviate extension of severe infection. The part is put at rest and suitable antibiotics are given.

Surgery may be particularly hazardous in irritated tissue of the perineum or external genitalia, anatomical sites known to tolerate radiation poorly because of the dangers of infection from constant contamination by feces and urine. Furthermore, areas of special caution, where tissues are susceptible to radiation, are the soles (Fig. 1), the palms, and the coverage (Fig. 2) over the sacrum or over the lower legs (Fig. 3).

Fig. 4 (Case 4).—Large slough of lower abdominal wall, in an area previously a port of heavy irradiation therapy for cervical carcinoma. Pelvic exenteration was performed and a colostomy brought out through a stab wound. The celiotomy incision (an ileal bladder constructed at the same time) was made through heavily irradiated wall. Debilitated patient died six months later of inanition in spite of massive supportive therapy and repeated attempts of rotation flap coverage.

3. SLOUGH

Necrosis with slough and infection (Fig. 4) jeopardize life. The devitalized tissue takes on a wet, dirty, gray, green, or yellow appearance and the area of slough daily becomes larger. Surgical débridement to good bleeding tissue is often necessary, but further slough may yet take place. Enzymatic débriding agents may hurry separation of dead tissue without further mechanical damage, but the granulation tissue at the cleaned-up base appears unhealthy and avascular. A skin graft rarely will be sufficient coverage here, and a flap is required, since it brings in its own blood supply.

4. EXPOSURE OF IMPORTANT STRUCTURES

Thin split grafts are usually the best assurance for wound coverages. They will take

Fig. 5 (Case 5).—*A*, recurrent fibrosarcoma of anterior shoulder attached to clavicle, subclavian vessels, and ribs. Area heavily irradiated. *B*, skin graft giving coverage directly on granulating surface of sectioned lung parenchyma. A flap would have given better and safer closure, was attempted but sloughed. Local tissues at same distance showed extensive radiation change.

Fig. 6 (Case 6).—A full thickness graft from the upper arm of a 62-year-old dentist, who had been holding in the dental x-ray films while "shooting" for many years, has only partially taken. After three weeks, there is some indolent granulation around islands of skin.

on exposed peritoneum, pleura, meninges, or viscera (Fig. 5) and keep the wound closed and, therefore, clean. Thick skin grafts applied to the cleanly excised base of apparent good blood supply may appear white or gray at the first dressing and have to be replaced later by a thinner split graft when a healthier and more vascular granulation can be produced in a few days. Full thickness grafts are risky on these doubtful bases (Fig. 6). Should a skin loss occur over tendons or bones, e. g., dorsum of the hand (Fig. 7), a pedicle graft is the only hope of salvage of tendon function. It should be employed early before the tendons are exposed and sloughing. Conservatism when sloughing tendons are present may be all that is possible, but the hand will be permanently quite stiff.

5. HEMOSTASIS

Bleeding from irradiation scar tissue cut across may be difficult to stop, as the cut vessel ends are held open and cannot retract, causing considerably more than the usual blood loss for the planned operation. If bleeding is minimal, owing to the dense fibrosis and obliterative endarteritis, fear of slough and infection is great. Secondary hemorrhage from such slough when involving a large artery, such as the carotid, subclavian, axillary, or femoral, is a real danger and can be rapidly fatal. Minor hemorrhage from smaller vessels or from telangiectases may be annoying but controllable by local pressure.

6. DIFFICULT DISSECTIONS

Dissection of important structures, as in the neck, axilla, groin, or parotid region, may be very difficult because of irradiation fibrosis and often must be done with a knife. Tissue planes are hard to find, and blunt fascial plane dissections cannot be readily done. Cutting firm, dense, fibrous masses from the adventitia of great vessels is fraught with the danger of entering the vessel. Fixed lymph nodes surrounded by scar but containing cancer may be cut into inadvertently.

7. CARCINOMA AND ITS SPREAD

Malignant disease arising so commonly in irradiated tissue is usually fairly well differ-

Fig. 7 (Case 7).—Loss of skin grafts with exposed tendons two weeks after excision of extensively irradiated skin from hands of a 64-year-old man, treated over 20 years before for a fungus infection. A Staphylococcus aureus infection and avascular tissues produced disastrous exposure with ultimately stiff rigid fingers. Pedicle graft from abdomen refused by patient.

entiated. The new growth is most frequently squamous-cell epithelioma and, therefore, metastasizes principally by lymphatics. These vessels are frequently blocked by extensive fibrosis, and the main cancer mass is incarcerated by a containing fibrous wall, forming a temporary barrier to spread. Because of this, lymph nodes are not involved until late and a regional node dissection is not necessary at the time of surgical excision of the primary cancer mass. Further irradiation should never be employed for carcinoma caused by x-rays or radium. Should the carcinoma be inadvertently cut across so that malignant cells are released to tissue planes beyond the fibrosis, there is often a very rapid spread locally. It is as though the growth potential of the carcinoma cells released were magnified several times. This possibility is likely the basis for a fairly widespread laymen's belief that cutting out a cancer will spread it and cause an earlier death. Every effort should be made to do a wide en-bloc removal and not to dissect near the malignant mass.

8. RADIO-OSTEONECROSIS

Bone damage due to irradiation poses special problems.[9] Minor trauma or slight infection often produces damage of great extent to the devitalized bone. The combination of osteomyelitis, radio-osteonecrosis, and carcinoma is a distressing one and may cause the loss of considerable bone. The jaws are especially prone to such damage, and large segments may sequestrate (Fig. 8). Either considerable radicalism, cutting back to good bleeding bone, is necessary to prevent further extension, or a very conservative "watch and wait" policy may be followed to save as much bone as possible. Dental extractions may be necessary but should be done with extreme gentleness and care. Massive antibiotic therapy will help. Extraction of teeth before radiation therapy is advocated by many [10] to prevent this complication.

Caution should be exercised in treating over cartilage, particularly of the nose or external ear. Minor trauma to these irradiated tissues may produce a smoldering chondritis which will not be controlled until a large portion of the cartilage and its avascular covering is removed and the wound healed.

9. INDUCED ALLERGIES

Allergies are easily induced in the devitalized irradiated skin which has been variously treated with ointments, local antibiotics, or other medicines. This complication may deny the use of a helpful medication in combination with surgery.

Fig. 8 (Case 8).—Extensive radio-osteonecrosis of mandible, with partial extrusion of sequestrum not well separated. Interstitial radium for carcinoma of floor of mouth had been given three years before.

10. PAIN AND NARCOTICS

The pain associated with infected irradiated tissue is described as boring, burning, agonizing, or intolerable. Excision of the involved tissue to good minute blood supply, whether or not immediate coverage may be possible, relieves such pain, but narcotic addiction, with its moral breakdown, lessening of pain tolerance, or the interpretation of other sensations as pain, may nullify the expected relief. Nerve blocks or sections will help, but pain may be the deciding factor in favor of extensive radical surgery, even though its chief effect is palliative relief.

Some of these derelict patients long on narcotics are among the most difficult with which one must deal.

11. INANITION

Depletion of the patient with a large open wound or irradiation defect is a very real danger.[8] As with a large open defect from trauma or thermal burn, the patient undergoes constant losses of blood, proteins, fluids, electrolytes, minerals, vitamins, and general good health. Patients die the gradual death of inanition from such large unclosable defects due fundamentally to irradiation changes. Coverage is the paramount factor for control, but the general build-up of the patient's nutrition, blood, and psyche may be necessary to allow wound healing. The vicious cycle of such losses may be hard to break.

SUMMARY AND CONCLUSIONS

1. Surgery contemplated in tissues previously subjected to irradiation should be planned with great care and tempered by judgment from the knowledge of the hazardous complications that may arise.

2. Infection, slough, uncoverage of important functional or vital structures, and poor wound healing are especially to be feared.

3. Excision of devitalized tissues should be carried out and early wound healing accomplished.

4. Coverage for good healing may require a skin graft or pedicled graft bringing in its own blood supply.

5. Infection should be prevented if possible by initial cleansing, gentle handling of tissues, excision to good blood supply, immobilization, drainage, and suitable antibiotics.

6. Surgery may best be deferred in some instances where to do it adequately would entail too great a risk from the hazards here described.

DISCUSSION

DR. D. P. SLAUGHTER, Chicago: I must commend Dr. Robinson for bringing this subject to our attention. I believe the plastic surgeons are more aware of this problem than are most of us general surgeons, and it is a very timely presentation.

This is an extremely important subject. Most of us as surgeons do not appreciate the destructive power of radiation. Radiation is one of the exceedingly important tools that our profession has in treating disease, and in my experience most of the problems that occur of the type Dr. Robinson has shown are due to the unintelligent use of radiation.

We should not consider this a castigation of the radiologist at all. The well-trained radiotherapist and the men who know what they are doing with radiation therapy do not produce these problems. It is the osteopath, the man who bought a machine without training, or the radiologist who is an excellent diagnostician and who also has a therapy machine, who does so. The good radiologists don't do this, either with radium or with x-ray therapy.

I see this as a problem mainly in two areas in the body: the head and neck region, where traditionally oral cancer has been treated by radiation. When cancer involves bone or when bone has to be involved in the radiation, there is a certain predictable percentage of osteoradionecrosis; moreover as the author has pointed out, radionecrosis particularly involves bone, which, incidentally, is more sensitive to radiation than soft tissue. Radionecrosis of bone and recurrent tumor is one of the worst problems we have. Many of these situations now are predictable in advance, and we are treating these primarily surgically and not secondarily after radiation recurrence.

The other place I see radionecrosis particularly is in trying to salvage recurrent pelvic cancer when heavy radiation has been used. There, I believe, at least prevention can help to some extent.

Dr. Robinson showed slides of midline problems from radiation. The midline should never be radiated if it is at all possible to avoid it, and it is always possible to avoid it in treating pelvic tumors. The angle approach should be used, and a lead strip should always be put over the midline so that if a laparotomy is required later it can be done through nonirradiated tissue, tissue that has been protected; that should always be done and is our practice.

[Slide] These slides emphasize the potency of radiation. Therapeutic radiation in cancerocidal doses should never be used below the elbows or below the knees. This man had a carcinoma of the dorsum of the hand treated by radiation, and this is purely the result of radiation. It is a radionecrosis right through the metacarpals and phalangeal joints requiring amputation, and is not a result of tumor at all.

[Slide] Another problem is radiation cancer, even of deep tissues. Ackerman has shown radiation sarcomas and fibrosarcomas, and here is a problem we have encountered. We have had seven or eight cases of radiation cancer of mucous membranes. This woman was treated for cervical tuberculous adenitis 20 years ago with low-voltage unfiltered radiation.

[Slide] She developed a carcinoma of the pyriform sinus. This is a low-power view showing the radiation change of telangiectasis and fibrosis of the submucosa.

[Slide] This shows carcinoma in radiated tissue. This is a radiated carcinoma of mucous membrane. We ordinarily think of it as occurring in the skin, but it does occur in deeper tissues.

Dr. Michael Mason, Chicago: We have been interested in radiation dermatitis and carcinoma for a long time, particularly as it occurs on the hand.

It occurs, as Dr. Robinson has shown, on many areas of the body. The areas which appear to be the most sensitive and which give us the most trouble are the hands, the soles, and the perineum, but there are many other areas as well.

We used to see it a great deal in roentgenologists. Now, of course, the professional roentgenologists are more careful. The older roentgenologists became martyrs to x-ray dermatitis. We see it a great many times in dentists. We see it in people who have been irradiated for epilation and for eczema on the hands and soles.

Just to emphasize the dangers of operating through this tissue carelessly, I have a few slides I would like to show of a person who was irradiated for itching, pruritus perinei. Something was wrong with the machine, and these irradiation burns occurred. The patient was seen at about this phase of his trouble, and the advice was given to excise the areas of dermatitis and apply skin grafts.

The irradiated skin was excised, but, unfortunately, instead of applying skin grafts, the areas were closed by suture and, of course, failed to heal and spread wide open.

[Slide] This shows the condition when he was admitted for treatment. The ulcers looked a great deal like the undermining burrowing ulcers described by Meleney. The person who first saw this case when he came to the hospital thought that was the diagnosis. The ulcers were excised and immediately grafted with skin.

[Slide] This shows that both healed very nicely under simple skin grafts.

[Slide] This microscopic section illustrates the fact that irradiation damage is actually to the cells of the skin. It was long thought that changes in this dermatitis were entirely on a vascular basis, but I believe the damage actually goes into the cellular structure. Here, in an early phase, is the dysplasia and hyperkeratosis so typical of the condition.

[Slide] This slide shows dyskeratosis and change in the polarity of the cells and in the actual structure of the cells.

[Slide] This shows gradual progression on to definite carcinoma.

[Slide] Here is the dense fibrosis which occurs beneath the skin, one reason why healing is very poor and one reason why carcinomas often remain localized to an area for a long time.

[Slide] This slide shows the fibrosis in more severe state, interfering with the blood supply, and gives a clue as to why healing in these tissues is extremely poor.

Dr. Paul Greeley, Chicago: I wish to bring out something about the "horrors" of excessive x-ray therapy. We never seem to see the end of the irradiation damage that ensues. Every week we see new patients with it. Where they come from we just don't know. I picked out a few of some of the horrible things we see, just so you will realize what some of them are.

[Slide] This shows a patient who had been treated for lupus erythematosus with a chronic radiation dermatitis. Obviously nothing can be done for her.

[Slide] This is a patient who was given radiation therapy for the removal of superfluous hair. You can't remove hair with radiation therapy except by giving lethal doses. Sooner or later the skin will break down into chronic radiation dermatitis. If the dermatitis goes long enough it will ulcerate, and in our experience approximately 50% of the radiation ulcers that we have removed have shown squamous-cell carcinoma changes. I am quite sure that percentage would be even higher if the patients didn't have the pain and the itching that drove them to surgery some time earlier.

[Slide] Here is the one person we have seen who was given radiation therapy for a hypophyseal tumor. She had a similar lesion on the other side. This degenerated into not a squamous-cell carcinoma but a spindle-cell sarcoma.

[Slide] Here is one which, of course, we did not operate on. X-ray therapy had been given for pelvic carcinoma with a complicating ulceration through the anterior abdominal wall into the bladder and with multiple fecal fistulae—completely inoperable.

[Slide] Here is another patient whom Dr. Cole and I operated on together. The patient had been given therapy for pelvic carcinoma and later developed an ulcer of the anterior abdominal wall with a small fecal fistula through the ulcer. Dr. Cole did a resection of the lower end of the ileum

and cecum and a lateral anastomosis of the two ends. We then closed the defect with adjacent tissue plus flaps which were interpolated from the side, such as you see here.

[Slide] This is a person who was given therapy for the treatment of a simple basal-cell carcinoma, which, as you all know as surgeons, is amenable to surgical excision very readily. Many times we have seen these around the nose and in the forehead, where not only do you have radiation necrosis of the soft tissues but also of the underlying bone. They are not simple problems to close because of the damaged vascularity.

[Slide] This was excised down to the underlying dura, and a temporary split-thickness skin graft applied. At a later date, for cosmetic reasons, we excised the graft and then carried the incision up and around the hair line across to the other side so that we were able to construct a large rotation flap. This was rotated over to the other side and closed by primary suture along hidden lines. Most of it is covered by the hair line, giving the patient a better cosmetic closure than one could do with a free graft.

DR. DONALD M. GLOVER, Cleveland: I wish to commend the fine discussion Dr. Robinson has given on this timely subject and to emphasize a couple of points.

One is the fact that remote irradiation effects on the skin are always the site of bacterial invasion, and in dealing with them we must assume that they are infected, even though the superficial ulceration may be minor. Without the benefit of prophylactic use of antibiotics the grafts are very likely to fail, at least in part.

Secondly, the vacular bed upon which these ulcers rest has been demonstrated in slides shown by Dr. Robinson and Dr. Mason. Perivascular round-cell infiltration, which is characteristic of radiation reaction of tissue, with ultimate fibrosis creates a very freely bleeding vascular bed that is somewhat misleading at the time of operation and quickly thromboses as soon as the operation is complete. However, this type of vascular bed does tolerate free grafting fairly well if excision has been adequate.

In persons with irradiation change of the skin we often have difficulty in determining exactly how far to excise. We don't like to sacrifice good skin, particularly on the hand and face, and we are a little conservative on the amount removed. Over a period of years other surrounding areas may undergo similar change, but the process is slow enough so that we have time to remove additional areas and to replace them gradually if we have missed them in the begining.

Finally, I believe the essayist and other discussants have pointed up the fact that irradiation is a very valuable agent, and, when we are using it to treat carcinoma that cannot be treated well in any other manner, we acept the radiation changes as an inevitable sequel which is entirely justifiable; but for the treatment of lesions which can be treated effectively otherwise it should be avoided.

REFERENCES

1. Hempelmann, L. H.: Acute Radiation Injuries in Man, Surg., Gynec. & Obst. **93**:385-403 (Oct.) 1951.

2. Lewis, S. R.: Management of Radiation Injuries, Am. Surgeon **18**:842-850 (Aug.) 1952.

3. Brown, J. B.; McDowell, F., and Fryer, M. P.: Surgical Treatment of Radiation Burns, Surg., Gynec. & Obst. **88**:609-622 (May) 1949.

4. Routledge, R. T.: The Surgical Problem of Local Post-Irradiation Effects, Brit. J. Plast. Surg. **7**:134-152 (July) 1954.

5. Teloh, H. A.; Mason, M. L., and Wheeloch, M. C.: Histopathologic Study of Radiation Injuries of Skin, Surg., Gynec. & Obst. **90**:335-348 (March) 1950.

6. Mason, M. L.: Irradiation Dermatitis of Hands, Am. Surgeon **17**:1121-1131 (Dec.) 1951.

7. Mason, M. L.: Irradiation Injuries of the Hand, Quart. Bull. Northwestern Univ. M. School **25**:51-59, 1951.

8. Converse, J. M.; Campbell, R. M., and Watson, W. L.: Repair of Large Radiation Ulcers Situated over Heart and Brain, Ann. Surg. **133**: 95-103 (Jan.) 1951.

9. White, W. C., and Finn, F. W.: Late Complications Following Irradiation of Pelvic Viscera, Am. J. Obst. & Gynec. **62**:65-74 (July) 1951.

10. Cutler, M.: Problem of Extractions in Relation to Osteoradionecrosis Complicating Radiotherapy for Intraoral Cancer, Oral Surg. **4**:1077-1090 (Sept.) 1951.

Fixation of Skin Flaps in Radical Mastectomy by Subcutaneous Sutures

Observations

BERNARD B. LARSEN, M.D.
and
CHARLES HUGAN JR., M.D., Cleveland

Cancer of the breast is the commonest malignant tumor in women, and radical mastectomy is the only proved method of cure. Anything that can be done to promote a quick and uncomplicated convalescence after this mutilating operation is important to these patients. It is agreed the operation must not be less radical if it is to be successful; so a lessened morbidity must come from improving the method of repair, or closure, of the wound.

The primary object of breast amputation for cancer is, of course, the radical, complete, and meticulous removal of the breast and adjacent structures in accordance with accepted techniques. Of secondary importance is closure of the wound, but this does not imply this part of the operation should be neglected. On the other hand, it should reflect the skill and the thoroughness of the primary amputation.

Primary healing is the aim in any clean surgical wound. This is no less true in radical mastectomy, but it is sometimes difficult to accomplish. Fluid tends to collect beneath the flaps, and dead spaces tend to occur in these large, extensive wounds involving the irregular, deep axillary fossa and the almost constantly moving chest wall. The ideal closure should hold the skin flaps securely to the deep structures without embarrassing the circulation to the skin or to the arm, without allowing fluid to collect beneath the flaps, without compounding the wound with a drain, and without interfering with early and extensive movement of the arm.

Halsted [1] modified and changed his operation with the problem of better closure, as well as adequate amputation, in mind. He pointed out that anything short of primary healing contributes to lymphedema of the arm. He advocated a short upper skin flap, the edge of which was sutured to the deep structures so as to cover the axillary vessels and obliterate the dead space in the axilla. Skin grafts covered the medial portion high into the axillary fossa.

For the most part, pressure and a drain have been relied upon to hold the skin flaps to the chest wall and axillary fossa. Orr [2] described fastening the skin flaps to the deep structures by sutures through the skin tied over short pieces of perforated rubber tubing. Leighton [3] and Keyes [4] have both described similar methods with through-the-skin sutures. Raffl [5] applied suction beneath the skin flaps. These various methods proved superior to pressure alone. Because of this, it seemed reasonable that subcutaneous sutures might prove to be even more efficient.

METHOD

After the amputation has been accomplished through the incision of choice, the arm is placed in extension, with the elbow bent, and

Submitted for publication April 25, 1955.

From the Department of Surgery Western Reserve University School of Medicine.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

Fig. 1.—The upper flap covers the axillary vessels and is fastened high in the axilla with subcutaneous sutures.

the wound is carefully closed, many subcutaneous fine cotton sutures being employed. These are first placed between the under side of the upper skin flap and the remaining clavicular portion of the pectoralis major muscle. The flap is next brought over the vital axillary structures and fastened to the fascia of the intercostal muscles and then to the fascia of the subscapularis and latissimus dorsi muscles (Fig. 1). Care is taken not to place sutures into vessels or nerves or in situations where they will cause direct pressure on these structures. The skin flap lies intimately, but not too tightly, in contact with the axillary contents so as to obliterate all potential dead spaces. Both flaps are finally fastened to the remaining chest wall by similar sutures, placed about 5 cm. apart, or wherever needed. Approximately 30 to 50 subcutaneous sutures of cotton are employed. Where the skin flaps are adequate, the skin edges lie in close approximation before they are actually sutured together (Fig. 2). If the skin flaps are inadequate, the edges are fixed to the chest wall by sutures and skin grafts are used to cover the defect. A drain is not used unless the wound is very wet. When the closure is complete, the arm is brought down, a moderate pressure dressing of fluffs is applied, and circulation is carefully checked. In two or three days a smaller simple dressing is put in place and held with adhesive straps fitted with ties.

CLINICAL MATERIAL

This series consists of 30 consecutive cases of radical mastectomy, closed by this method, on private patients (B. B. L.). These cases were not selected in any way except that they conformed to the accepted indications for radical mastectomy. During the course of this series simple mastectomy was done in five other cases of carcinoma for various reasons, but these are not included in this report.

The patients were from 38 to 79 years of age. One-half of the lesions were in the upper outer quadrant of the breast, one-fourth in the upper inner quadrant, and the rest in the areolar area or lower quadrants. There were 19 left and 11 right radical mastectomies. In only one was a drain inserted. In one case a skin graft was used. Most patients received 1, but a few 2, units of blood. In no patient did the blood pressure fall to shock level either during or after surgery. The placing of the subcutaneous fixation sutures added 20 to 30 minutes to the oper-

Fig. 2.—The dimples in the skin are where 30 to 50 subcutaneous sutures fasten the skin flaps to the deep structures.

ating time. All patients received antibiotic medication after surgery.

RESULTS

In 21 of the 30 cases there was no pocketing of serum or blood. In four cases 20, 25, 30, and 50 cc. of serum were aspirated once. In three aspiration was done twice, and in one, three times, averaging less than 30 cc. per aspiration. There was a hematoma in one wound. This became infected, and so it was evacuated and drained. In none of these cases was the axilla involved.

In 24 of the 30 cases the postoperative temperature did not go above 100.4 F (38 C), and in the remaining 6 the average highest elevation was 101.1 F (38.4 C). All temperatures were normal by the third postoperative day with but one exception.

Postoperative swelling of the arm was not troublesome. In 6 cases there was none; in 18 it was slight, and in 6 it was moderate. In no case was it severe. Within several weeks no arm was more than ½ in. larger in circumference than the normal.

Early movement of the arm was classified as good (75% or more) in 23, fair in 6, and poor (less than 50%) in 1. The range of motion tends to lessen during a period of from two weeks to two months after surgery; then it is regained. Extension is 75% to 100% in all patients of this series operated upon at least 6 months ago and practically 100% in all patients operated upon at least 12 months ago (Fig. 3).

In the 30 cases there were no serious complications and no deaths. One patient developed pneumonitis on the 10th postoperative day, after an uneventful recovery to this point.

There were only four cases with significant skin slough, although there were several others with superficial sloughs along a short portion of the skin edge. In the four cases with significant slough one was in the infected case, and this resulted in a granulating area 10 cm. long and 6 cm. at its widest point. Another patient, from whom 50 cc. of serum was aspirated, had a skin separation with slough resulting in a granulating defect 5×3 cm. In one case there was a very superficial slough 5×2 cm. along the edge of an extremely wide lateral skin flap made necessary by the unusual position of the tumor. The only significant axillary slough was approximately 1 cm. in diameter.

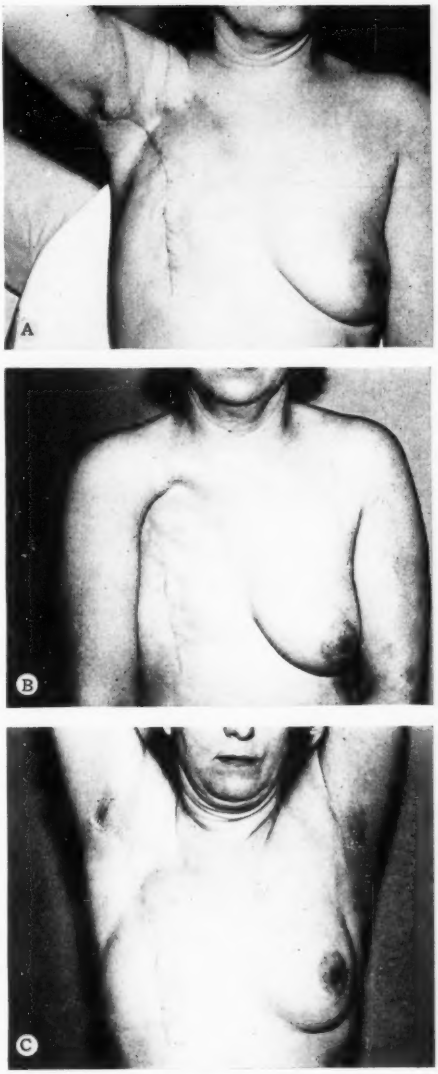


Fig. 3.—*A*, 10 days after operation. Primary healing throughout. *B*, 11 months after operation. *C*, 11 months after operation. Complete range of movement.

Discoloration of the upper arm was marked in one obese patient and rather extensive in several others. This complication was mainly cosmetic and did not lead to lymphedema of the arm.

At this writing all patients are alive. Two have metastatic lesions. The first operation in this series was done about 20 months ago.

COMMENT

The subcutaneous fixation of the skin flaps following radical mastectomy proved to be a very satisfactory procedure.

The one infected case is worthy of mention. This was the fifth in the series. The wound was very wet, and the skin flaps were meager because of an extensive lesion. The wound should have been drained but was not. A skin graft should have been used but was not. It is significant that even in this case healing in the axilla was by primary intention, movement of the arm was excellent, and the slight swelling of the arm which occurred soon disappeared, not to return.

In all cases there was no pocketing of serum in the axillary region. Subcutaneous sutures seemed to have solved this problem in this troublesome area without the use of drains. Loss of 300 to 500 cc. of serum by suction or by drainage was thus avoided. Where pocketing of serum occurred on the chest wall an additional stitch or two might well have prevented this minor complication.

Skin slough was much less than we have experienced with other methods. The blood supply to the flaps, though they may have been broad, seemed unusually well-maintained. The fact that the flaps are fixed primarily by their underside and quickly become adherent contributes to this favorable situation. Also, the tension in the skin flaps is distributed over many subcutaneous sutures instead of over the skin-edge sutures alone. Then, too, the blood supply to the flaps is not embarrassed by excessive external pressure. Dressings of this type are not needed. There is no tendency for the subcutaneous sutures to cause pressure necrosis of the skin as is seen in the through-the-skin types of fixation sutures.

The ability of these patients to move the involved arm extensively is accounted for, in some measure at least, by the placing of the arm in extension when the skin is fixed in the axillary fossa. Then too, all cases healed by primary intention in the axillary region. On the other hand, the suturing of the skin with the arm extended causes a certain amount of puckering and folding of the skin in this region which is at first unattractive but which irons out smoothly, with a good cosmetic result when healing is complete.

The tendency toward lymphedema of the arm was minimal, owing to primary healing in the axilla in this type of closure, in contrast to the more marked inflammation and fibrosis which occurs when there is pocketing of serum or blood in a dead space or when there is infection. With these excellent early results it is only reasonable to assume that lymphedema will not develop in the future unless there is local recurrence or excessive fibrosis due to x-ray therapy.

Discoloration of the arm was very marked in several of the earlier cases. Without fixation sutures the blood and serum from the wound in the upper arm drains freely into the axillary fossa, but when subcutaneous fixation sutures are used this avenue of escape is less open. We are now careful to leave a small fringe of the pectoralis major muscle at its insertion so that bleeding points may be more certainly tied. With this technical precaution discoloration of the upper arm has been, for the most part, avoided.

The 20 to 30 minutes needed to secure the skin flaps to the deep structures, with 30 to 50 subcutaneous sutures, is time well spent. This effort contributes to the smooth, more prompt, and less disabling recovery of these patients.

CONCLUSION

Ideally, skin closure following radical breast amputation should hold the skin flaps to the deep structures without embarrassing the circulation to the arm or to the skin flaps, without pocketing fluid beneath the flaps,

without compounding the wound with a drain, and without interfering with the early and extensive movement of the arm. Careful fixation of the skin in the axilla and on the chest wall with subcutaneous sutures approximates this ideal and leads to a rapid, uncomplicated convalescence after radical mastectomy.

REFERENCES

1. Halsted, W. S.: Developments in the Skin-Grafting Operation for Cancer of the Breast, J. A. M. A. **60**:416, 1913.

2. Orr, T. G., Jr.: An Incision and Method of Wound Closure for Radical Mastectomy, Ann. Surg. **133**:565, 1951.

3. Leighton, W. E.: Technic for Radical Mastectomy, Arch. Surg. **61**:312, 1950.

4. Keyes, E. L.; Hawk, B. O., and Sherwin, C. S.: Basting the Axillary Flap for Wounds of Radical Mastectomy, A. M. A. Arch. Surg. **66**:446 1953.

5. Raffl, A. B.: The Use of Negative Pressure Under Skin Flaps After Radical Mastectomy, Ann. Surg. **136**:1048, 1952.

6. Larsen, B. B.: The Fixation of Skin Flaps by Subcutaneous Sutures in Radical Mastectomy, J. A. M. A. **159**:24, 1955.

The Exposure Method of Burn Treatment

Observations With Particular Reference to the Use of Hydrocortisone

CARLYLE E. WILSON, M.D.
KENNETH F. KIMBALL, M.D.
and
SAMUEL A. SWENSON JR., M.D., Omaha

The management of the burn wound has recently undergone a revision in principle in the minds of many investigators. The "closed," or "pressure," dressing has been supplemented by the "exposure," or "open air," technique. The latter is neither new nor by any means the most popular concept today. Not all burns should be handled by the exposure method. The closed method is utilized primarily for extensive circumferential burns. The value of topical sprays and ointments as an adjunct to the exposure method is questioned. The use of a hydrocortisone antibiotic ointment in the closed method appears to be of value in selected cases, as does the use of parenteral hydrocortisone.

The exposure method of burn treatment is not new. The first reference to this method in the American literature was that of Copeland,[1] in 1887. From that time until 1949 there were only occasional references to this technique in the literature. Each of these authors, surprisingly, was very favorably impressed with this technique, and each was astonished that the method was not more universally employed. The main stimulus for the revival of the exposure technique has been the recognition of deficiencies of the closed method where there are mass casualties. World War II and the Korean conflict revived the interest in this technique. Civil disasters, such as the Texas City incident, also contributed stimulus for renewed interest in this method. Recent investigators reporting on this subject have been Wallace,[2] of Scotland, Pulaski[3] and Artz,[4] of the United States Army, Blocker,[5] of the University of Texas, and Pemrik and Musselman,[6] of Detroit. Their results and methods differed little, and their conclusions were similar. They felt that this was the only practical method yet devised for coping with mass burn casualties. This presentation is an evaluation of our results with the exposure method and with the use of hydrocortisone.

Received for publication April 25, 1955.

Supported by a research grant from the Upjohn Company, Kalamazoo, Mich.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

CLINICAL INVESTIGATION

The exposure method has been used by us for the past three years. More than 50 second- and third-degree burns have been treated in this manner. Experience with the closed method had been satisfactory, except for the deep second and third degree burns where infection soon became a major problem. The occasional apparent conversion of deep second degree burns into third degree burns was particularly impressive. An additional disconcerting fact was the frequent observation of a relatively low percentage of take of skin grafts, in contrast to the usual satisfactory takes, particularly where suppuration was present. It seemed that the exposure method might reduce the incidence and severity of infection in burn wounds. Use of the exposure method of treatment was then instituted in all burn cases under our care. The only exceptions made were relatively small burns where exposure treatment would incapacitate the patient economically. All age groups were included. The initial management of the acute burn was the same as was

used in the closed method, the management of burn shock, fluid, electrolyte, and blood replacement being essentially the same. The burn patient was admitted to the hospital and taken to the operating room if the burns were extensive and severe. If they were neither extensive nor severe, the patient was taken directly to his room. In either instance the patient was placed upon clean sheets on his back or his abdomen, as dictated by the location of the burn. If there were gross contamination and devitalized tissue, the burn was gently washed with hexachlorophene soap solution. This was followed by saline irrigation. In practically every instance this was carried out under analgesia without the necessity of general anesthesia. Normal room temperature was maintained, with particular care to avoid drafts. Any pain present was controlled with the use of intravenous analgesics. Where there were complete circumferential burns of the trunk, it soon became apparent that the closed method was preferable. With burns of arms or legs, it was often possible to leave them exposed by special sling and pulley arrangements.

After a period of about 72 hours, the burn would develop an eschar of coagulated serum that was dry, firm, and adherent. The crust of partial-thickness burns desquamated in 7 to 14 days and in deep partial-thickness burns, in 14 to 28 days (Fig. 1). The eschar

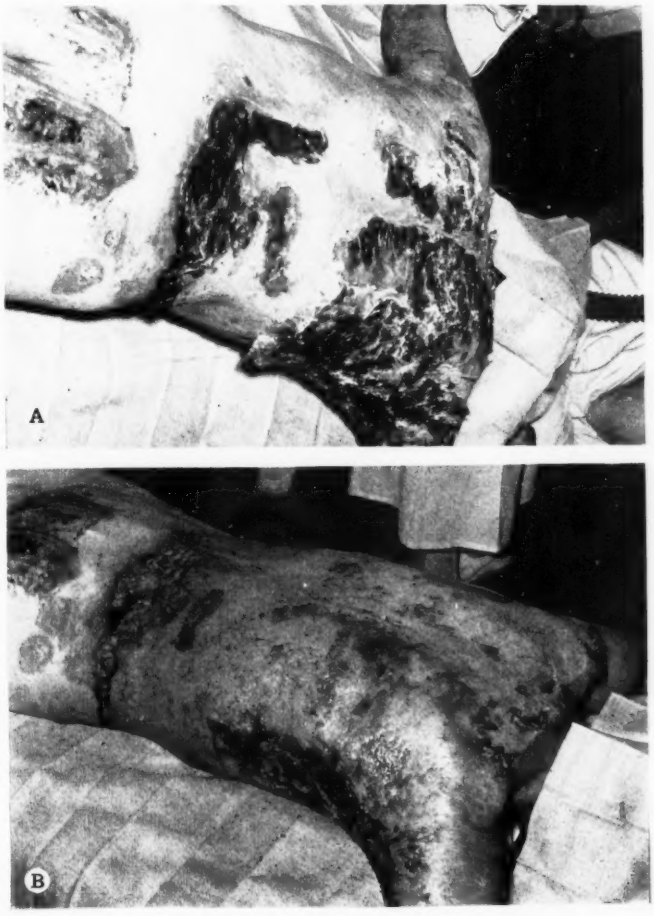


Fig. 1.—*A*, before eschar is removed. *B*, after eschar is removed.

in full-thickness skin loss was depressed and adherent to underlying tissue. Any need for analgesia during the second 24-hour period was minimal, inasmuch as the burn wound was essentially sealed off from the air by this crust. Every attempt was made to maintain the crust in a completely dry state.

During the course of the next several days, the patient was encouraged to become ambulant. When joints, particularly the hands, were involved, it was often necessary to apply a thin coating of sterile ointment to prevent cracking of the eschar. If cracking developed, the devitalized tissue immediately adjacent was débrided. With the occasional development of infection in such an area, the wound was dressed with fine-mesh gauze moistened frequently with sterile isotonic saline. Daily soaks in hexachlorophene solution in tub or whirlpool bath were instituted if larger areas of infection developed.

Healing was sufficiently complete in second-degree burns that the patient could be dismissed by the 14th day. Deep second-degree burns, depending upon the location, required several additional days hospitalization. When third-degree burns were present, an average of 21 days elapsed before the burn wound became suitable for grafting. Skin grafts were routinely enclosed with pressure dressings. Where infection became a problem and the area to be grafted was relatively immobile, grafts were left exposed. This method was used routinely for grafts on the face. Exposed grafts were periodically saturated with saline to prevent dryness.

The effect of topical hydrocortisone on partial and full thickness burn wounds in the form of ointment, both plain and in combination with neomycin, was investigated. Hydrocortisone was applied two to four times daily from the day of burn up to 21 days in the form of a 1% acetate compound.* This was used in burns which were suitable for comparison, controls being carried out in adjacent portions of the burn or on the opposite extremity.

LABORATORY INVESTIGATION

Comparable burns were made in 25 rats by the use of a temperature-controlled hot iron. Both partial and full-thickness burns were inflicted on either side of the midline on the back of rats of comparable age, weight, and nutritional status. One side was used as a control and the opposite side for applications of one of the following ointments: (1) hydrocortisone, (2) hydrocortisone antibiotic combination, and (3) the ointment base for (1) and (2). The applications were made twice daily for periods up to three weeks. Biopsy specimens were obtained at varying periods to show the comparison. Histologic study was then carried out. The tissue sections were evaluated on the basis of (1) the degree of burn, (2) inflammation, (3) granulation tissue response, and (4) reepithelization. The degree of burn was based on the presence or absence of both covering epithelium and skin appendages. Inflammation was graded from 1+ (minimal) to 4+ (abscess formation). Granulation tissue was classified from minimal to exuberant. The degree of reepithelization was determined by both linear and perpendicular regrowth as measured microscopically. The results are shown in the Table.

COMMENT

Any burn that cannot be completely exposed to the air should be treated by the closed method. Small areas which cannot be exposed may be covered with partial pressure dressings and the remaining major portion of the burn exposed. Experience has shown that the element of pain in the exposed burn wound has been overemphasized and overestimated. The advantage of frequent observation of the burn wound has been most important. It was not found necessary to in-

* Cortef and Neo-Cortef, supplied by The Upjohn Company, Kalamazoo, Mich.

Comparison of Results in Similar Burns on Fifty Rats

	Neo-Cortef	Cortef	Ointment Base	Control
Epithelization	Moderate *	Moderate *	Moderate *	Moderate *
Inflammation	Moderate	Minimal	Minimal	Minimal
Granulation	Minimal	Minimal	Moderate	Moderate

* No significant difference.

corporate the hands in pressure dressings, for mobility of joints was extremely important at this stage. Exposure with motion and elevation resulted in rapid diminution of edema. Hands maintain themselves essentially in the position of function when exposed. Exposed patients not burned extensively and severely were ambulated early. Patients able to care for themselves in regard to eating and bathroom requirements maintained a surprising morale not seen in the burn patients encumbered in massive dressings. Decrease of odor contributed to the morale and appetite of the patient. The relative absence of infection with this method, as contrasted with the closed method, again contributed to the maintenance of a normal appetite. As a result of decreased surface infection, the severity of the toxic phase was diminished. Joints and, particularly, the dorsum of hands, were grafted first and as early as possible.

Experience to date has indicated that in many instances the burn in the dry state heals more rapidly. The explanation for this is the difficulty of avoiding maceration when any type of ointment is used. Maceration is always associated with increased tendency toward infection. Figure 2 illustrates the maceration and infection with ointment on the left leg. At present, investigation is being carried out regarding the efficacy of fine-mesh gauze impregnated with hydrocortisone antibiotic ointment on the burn that is in the process of being grafted whether infection is present or not. Hydrocortisone and neomycin maintain their activity after being subjected to autoclave temperatures. This maintained activity may prove to be of value. A report will be made on this at a later date. Although the present cost of such ointment is relatively high, its use may be rationalized on the basis of decreased hospital and operating-room time.

Rhoads [7] estimated that 60% of the persons injured in an atomic disaster would have thermal burns. Pearse,[8] in evaluating the single atomic explosion at Hiroshima, estimated that for the 34,000 burned patients in that disaster, 170,000 professional persons and 8,000 tons of equipment would be needed

Fig. 2.—*A*, immediately after burn. *B*, two weeks after burn.

to properly administer the closed method and care for those casualties. It is our opinion that if the closed method were to be used in the treatment of mass burn casualties, whether they be civil or military disasters, burn centers would have to be organized before any such disaster. In the case of an atomic explosion in a major city, several perimeter hospitals would have to be set aside exclusively for burn patients, with large numbers of doctors, nurses, and aides assigned to

each. There also would be a necessity for stock-piling a tremendous amount of equipment in various perimeter warehouses for the emergency. It seems quite logical that mass burn casualties can be more effectively treated by the exposure than by the closed method.

There have been many liquids, powders, and ointments advocated for use in the management of burn wounds. These have been primarily in the form of agents to produce suitable eschar or to promote healing in one manner or another. Ponka and Lam [9] have shown the lack of value of various topical agents in either the reduction of infection or stimulation of healing of cutaneous wounds. Blocker [10] recommends the use of neomycin on the infected burn. As an adjunct to the hexachlorophene soaks in control of infection in the exposure method, we have used topical antibiotic powder with satisfactory results. It is our opinion that, in general, the less done to the burn wound, the less healing is retarded.

In recent years there has been an increased interest in the effect of corticotropin (ACTH) and cortisone parenterally in the management of burn wounds. Evans [11] believed that there is an occasional necessity for the use of cortisone or corticotropin in the burn injury with insufficient stress response. The majority of these reports have been quite favorable. The patient in burn shock who exhibits symptoms of adrenal insufficiency will benefit from the administration of intravenous hydrocortisone. The patient with extensive severe burns who shows symptoms of adrenal exhaustion during the grafting stage may be a candidate for short-term hydrocortisone therapy. Recent work does not substantiate earlier claims for improved epithelization.

SUMMARY AND CONCLUSIONS

The advantages of the open method of burn treatment are these: (1) mass casualties can be managed more effectively; (2) the incidence of infection is lower; (3) the deep second-degree burn is not converted into a third-degree burn by maceration and infection; (4) the morale and the appetite of the patient are maintained; (5) nursing care is reduced; (6) offensive odors are minimized; (7) the necessity for dressing changes is eliminated, along with the necessity for general anesthesia; (8) frequent observation of the burn wound is possible, and (9) the element of pain is minimal.

The following are contraindications to the exposure method of burn treatment: (1) extensive circumferential burns, (2) small burns that can be closed, returning the patient to his normal economic status, and (3) the necessity for transportation of severely burned patients over long distances. All other burn wounds may be treated more effectively by the exposure method than by the closed method.

Topical application of hydrocortisone ointments exerts no beneficial effect upon the burn wound. Local antibiotics may reduce surface infection if maceration is avoided. Systemic hydrocortisone is of proved value in cases of adrenal insufficiency.

DISCUSSION

Dr. Conrad R. Lam, Detroit: The first time the Central Surgical Association met in this room, 13 years ago, Dr. Brush and I read a paper entitled, "The Effect of the External Application of Some Substances to the Healing of Cutaneous Wounds."

We had investigated about 10 of the old standbys, such as scarlet red and vitamins A and D ointment, and concluded that it made no difference what was put on a wound. I am rather glad to see that 13 years later the authors of this paper have come to almost the same conclusion in regard to local steroid therapy.

The discussion might proceed along two lines. The first is whether or not the exposure method for the treatment of burns should be used. I should not want to get into an argument with our Chicago friends about this. However, anything that is being taken over and that is liked by so many people must have some advantages. Dr. Clifford, at our hospital, now uses it in practically all his cases.

The evidence for the use of steroids for local application or for general application seems to be rather meager. I should judge that, since reviewing the data, the authors were unable to sustain one conclusion in the abstract—that there are certain indications for the local application of hydrocortisone. Perhaps in rebuttal they may enlarge on that a bit.

Dr. Samuel A. Swenson Jr., Omaha: We believe the main indication for application of topical hydrocortisone was that of a possible reduc-

tion in inflammatory or fibroplastic response in the granulation areas, particularly in waiting, in that the area might become best suited for grafting.

We believed that perhaps there was a decrease in the exuberance of the granulations by the use of topically applied hydrocortisone. Necessarily, the addition of the antibiotic topical hydrocortisone, we believed, had some part in reducing surface infection.

DR. JOHN BELL, Chicago: We realize that, regardless of the method initially embraced in the treatment of burns, this is only one phase of the burn treatment. Irrespective of whether open or closed methods are used, maceration is always a great danger. If one properly applies a compression dressing, however, one should encounter no maceration. In our experience the use of compression dressings has obviated the necessity for narcotics, as the patients are entirely comfortable.

In the event of mass casualties, many patients having burns of the extremities can be managed as ambulatory patients if a compression dressing is properly applied. It would not be possible, however, to manage such patients on an ambulatory basis if the open method were used.

I should like to ask here when and how the necrotic tissue was removed from the young patient shown in the slides. In similar cases of our experience, we have removed such necrotic tissue by surgical excision in from five to seven days following the burn and have started skin grafting within two weeks after the burn, because we believe that if this necrotic tissue is allowed to remain for three weeks before removal there is much greater danger of infection.

DR. WILLIAM ALTEMEIER, Cincinnati: Lest anyone here get the idea that cortisone or corticotropin (ACTH) can be used systemically in the management of burns without the danger of invasive infection developing, I am bringing this point to your attention.

In burns of any extent, and particularly deep second degree or third degree, I think there is a distinct possibility of an invasive infection developing from the area of the burn to the physiologic interior of the body during corticotropin or cortisone therapy.

Early in the steroid period, we made this mistake and lost a patient from invasive infection which developed in the absence of localized or usual general signs associated with infections.

When the report reached us that infection did not develop in burned areas treated by the exposure method, our investigations revealed the following facts:

Infections by the Gram-negative organisms such as Pseudomonas aeruginosa (Bacillus pyocyaneus) were less obvious in burned areas treated by the exposure method because the eschar was kept dry, insufficient moisture being present for the growth of these organisms. Consequently, the bluish-green pus was not in evidence. However, close inspection of the burned eschar revealed definite evidence of infection. The anaerobes and the pyogenic cocci grew prolifically beneath the eschar in localized abscesses. Biopsies showed the organisms to be present and an inflammatory reaction to be much in evidence. Moreover, three cases of septicemia were noted in these patients, two of which were unrecognized and two of which were receiving cortisone therapy simultaneously.

It has been computed by Evans that a 50% burn produces the maximum stimulation to the adrenal cortex. Consequently, corticotropin is probably of no benefit. Others feel that the dangers attending the systemic administration of cortisone are too great to warrant its use during the early postburn period.

I have had no experience with the topical use of hydrocortisone ointment with or without neomycin. My remarks are directed only toward the systemic administration of cortisone in patients with severe burns.

DR. MICHAEL MASON, Chicago: I didn't mean to come up a second time, but I just want to say one word about the open treatment of burns on the hands.

Whatever I might think about open treatment for other areas I shall not say, but in my opinion the hand is one place where the open treatment is not indicated.

DR. CARLYLE E. WILSON, Omaha: First of all, may I thank Dr. Lam and Dr. Swenson for their discussion, and Dr. Mason, Dr. Bell, and Dr. Altemeier for their questions. The questions are very pertinent.

In answer to Dr. Bell's question regarding when the débridement was carried out on the 12-year-old girl, we have the opinion that sometimes débridement is carried out a little too early. We have been fooled several times in débriding a deep second-degree burn that would have healed without grafting. I think all of us at some time or other have difficulty distinguishing between a deep second-degree burn and a third-degree burn; so we feel that caution should be exercised in that regard, lest unnecessary grafting be carried out.

We removed the necrotic tissue by sharp dissection and also with the use of the whirlpool bath.

I should like to thank Dr. Altemeier for his comments. I wish to reemphasize that in our opinion the only possible place for parenteral or systemic steroid therapy is in the extensive, severe burn, late in the course where there is an evidence

of adrenal insufficiency, and then and only then short-term hydrocortisone therapy, just to supplement the exhausted adrenal cortex. Perhaps four or five days would be sufficient.

REFERENCES

1. Copeland, W. P.: The Treatment of Burns, M. Rec. **31**:518, 1887.

2. Wallace, A. B.: Treatment of Burns: Return to Basic Principles, Brit. J. Plast. Surg. **1**:232, 1949.

3. Pulaski, E. J.; Artz, C. P.; Schaeffer, J. H.; Buckabee, W. E.; Mitchell, R. C., and Russell, J. P.: Exposure (Open) Treatment of Burns, U. S. Armed Forces M. J. **2**:769, 1951.

4. Artz, C. P.; Reiss, E. P.; Davis, J. H., and Amspacher, W.: The Exposure Treatment of Burns, Ann. Surg. **137**:456, 1953.

5. Blocker, T. G., Jr.: Local and General Treatment of Acute Extensive Burns: Open Air Regime, Lancet **1**:498, 1951.

6. Pemrick, T. D., and Musselman, M. M.: The Management of Burns, S. Clin. North America **33**:1127, 1953.

7. Rhoads, J. E.: Mass Treatment of Burns, Pennsylvania M. J. **56**:191, 1953.

8. Pearse, R. E.: Burns, J. Missouri M. A. **18**:323, 1921.

9. Ponka, J. L., and Lam, C. R.: Effect of Application of Several Antibacterial Substances on Healing of Wounds, Arch. Surg. **59**:57, 1949.

10. Blocker, T. G., Jr.; Snyder, C. C., and Lewis, S. R.: The Late Treatment of Severe Extensive Burns, South. M. J. **47**:371, 1954.

11. Evans, E. I.: Early Management of the Severely Burned Patient (John Chalmers DaCosta oration), Surg., Gynec. & Obst. **94**:273, 1952.

Experimental Evaluation of Prolonged Hypothermia

BERNARD FISHER, M.D.
CLEM RUSS, Ph.D.
EDWARD FEDOR, Ph.D.
RALPH WILDE, M.D.
PERRY ENGSTROM, M.D.
JOHN HAPPEL, M.D.
and
PAUL PRENDERGAST, B.S., Pittsburgh

At present, hypothermia is used in cardiac surgery and other situations where there is deliberate temporary interruption of major blood supply for short periods of time.* Its value in conditions where reduction in metabolism and "physiologic" hypotension would be desirable has been suggested.† Acute pulmonary disease, emboli, anemic crises, lower nephron oliguria, shock, myocardial infarction, and thyrotoxicosis are but a portion of the list presented by Swan [7] in a notable critique of the present status of hypothermia where the value of this procedure might be speculated upon.

For use in such situations, it is conceivable that prolonged hypothermia might be resorted to. Further, the occasion may well arise where hypothermia for surgery may by necessity be extended beyond the relatively short periods of time now in use.

Submitted for publication April 25, 1955.

Aided by Department of the Army Grant, DA-49-007-MD-518 and Public Health Grant H-2065.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Department of Surgery, Section on Surgical Research, and the Addison H. Gibson Laboratory, University of Pittsburgh; John and Mary Markle Scholar and Assistant Professor of Surgery, University of Pittsburgh (Dr. Fisher).

* References 1 to 4.

† References 5 and 6.

Although in recent years there has been much fundamental investigation upon hypothermia, most of the experiments have been concerned with methods of cooling, reduction of temperature to lower levels than previously obtained, and the immediate metabolic effects of the cooling and rewarming process. Few observations on the effects of prolonged hypothermia have been reported. The majority of these concern themselves with patients subjected to general hypothermia. Its use in the treatment of cancer was first described by Smith and Fay ‡ in 1939-1940, when patients were maintained at rectal temperature levels of 29 to 32 C for as long as five days. Dill and Forbes [10] and Talbot [11] reported on schizophrenic patients subjected to hypothermia up to 60 hours. For the most part, the observations reported upon in humans were made under such variation of body temperature that little conclusive information is obtained. In the experimental animal, Woodruff [12] maintained 13 dogs below 27 C for an average of 7¼ hours (one animal 26 hours) and concluded that dogs were unable to survive hypothermia sufficiently long enough to make protracted metabolic studies feasible. Bigelow, Lindsay, and Greenwood,[13] although not reporting any specific observations, did maintain two dogs cooled to 20 C for 17 and 20 hours until death. Recently, Spurr, Hutt, and Horvath § reported a series of 13 animals maintained at low body temperatures for an average of about 10 hours. They concluded that cardiac and respiratory rates, pulmonary ventilation, ventilation equivalent, and oxygen consump-

‡ References 8 and 9.

§ References 14 and 15.

TABLE 1.—*Fate of Twenty Dogs Subjected to Prolonged Hypothermia*

Dog No.	Length of Hypothermia, Hr.	Weight, Kg.	Temperature, C		Time in Bath, Min.	Temperature After First Hr., C	Fate of Animal
			Placed in Bath	Removed from Bath			
443	22.0	24.5	39.0	29.0	67	23.4±0.6	Died, ventricular fibrillation
720	31.5	12.5	36.0	31.0	12	24.2±0.4	Continued hypothermia
745	24.5	6.8	38.0	30.0	18	25.0±0.1	Died 6½ hr. after rewarming
751	24.0	13.6	38.5	28.5	22	23.5±0.6	Died, cardiac arrest
761	21.0	10.3	37.8	29.2	25	23.1±0.6	Survived rewarming
784	11.5	8.2	38.0	29.9	12	24.3±0.4	Continued hypothermia
787	16.5	8.0	36.9	29.7	15	24.1±0.5	Died, ventricular fibrillation
789	20.0	7.2	37.0	29.0	16	23.0±0.5	Died 4½ hr. after rewarming
790	24.0	7.1	38.1	29.9	16	24.9±0.6	Died 12 hr. after rewarming
850	12.5	12.5	38.0	29.0	17	24.0±0.9	Continued hypothermia
868	19.0	14.7	38.0	29.5	29	23.9±0.5	Continued hypothermia
888	9.2	16.8	38.0	30.0	28	24.5±0.6	Died, ventricular fibrillation
903	23.5	15.3	37.5	28.5	24	23.2±1.0	Died, respiratory failure, cardiac standstill
906	10.5	18.0	40.0	29.0	54	22.3±0.4	Died, ventricular fibrillation
912	6.5	11.6	36.0	28.5	25	22.3±0.7	Died, ventricular fibrillation
916	26.0	18.4	35.3	26.0	36	23.0±0.9	Died, respiratory failure and fibrillation arrest
931	8.5	18.7	38.5	27.0	32	23.5±0.6	Cardiac arrest
947	6.5	17.6	38.0	29.0	40	22.6±0.2	Died, fibrillation
960	21.5	17.0	40.0	29.0	32	23.8±0.6	Died, respiratory failure and fibrillation
968	12.5	14.5	38.5	29.0	19	23.9±0.7	Died, fibrillation
Average	16.8 (6.5-31.5)	31.6	37.8±1.1	29.3±1.0	27	23.5±0.7	

tion did not exhibit the marked constancy seen in rectal temperatures during the period of stability.

It would thus seem that before resorting to prolonged hypothermia clinically, more fundamental knowledge is needed concerning this modality. It is the purpose of this paper to report some of our observations made upon 20 animals maintained hypothermic for an average of 16.8 hours (6.5 to 26 hours) (Table 1).

Further, since ether anesthesia was used exclusively in this series, the effects of this anesthetic agent will be elaborated upon. Practically all investigations in hypothermia have been done with pentobarbital sodium anesthesia, and it remains to be proved to what degree reported results are influenced by this agent.

METHODS

Mongrel dogs of both sexes, averaging 13.6 kg., were used. A standard routine preparation of all animals was followed. Preliminary blood samples were taken for the following: hematocrit, by centrifuging for 20 minutes at 3500 r. p. m. in Wintrobe tubes; plasma specific gravity, determined by the copper sulfate technique of Phillips, Van Slyke, and co-workers [16]; prothrombin time, by the use of "Simplastin" (Warner-Chilcott); coagulation time, by a modified three-tube Lee White method; serum Na and K, analyzed by Barclay flamephotometer; serum chloride,‖ calcium,[18] and phosphate [19]; total protein, albumin, and globulin ¶; blood and urine pH, read by Beckman pH meter; blood and urine sugar [22]; O_2 content of blood,# and CO_2 content of plasma.* Blood samples for CO_2 were collected under oil, immediately centrifuged, and the plasma drawn off under oil. Animals were anesthetized with open-drop ether and maintained in a light plane of anesthesia while radiopaque catheters were placed under fluoroscopic guidance through the external jugular vein into the right ventricle at its apex and deep into the hepatic vein of the liver. They were anchored in place at the skin level. Saline solution, at a rate of 1 to 2 drops a minute, was permitted to drip for several hours through the catheters, which were used for determination of cardiac output and hepatic blood flow, the results of which are the subject of a future report. No anticoagulant was given any animal. Catheters were passed through the femoral artery and vein so that they lay in the aorta and inferior vena cava at the level of the diaphragm. Blood pressures were read by attaching a mercury manometer to the femoral arterial catheter, and venous pressures were obtained from a saline manometer connected to the

‖ Reference 17, p. 838.

¶ References 20 and 21.

Reference 17, p. 257.

* Reference 17, p. 245.

femoral venous catheter. No attempt was made to measure exact venous pressure, but the relative position of the manometer to the dog was maintained constant throughout the experiment. Thus, relative changes in venous pressure were obtained. The precooling reading was taken as the zero point. A soft rubber catheter was inserted into the urinary bladder. Electrocardiographic leads were secured to the left arm, left leg, and precordium. Temperatures were obtained by inserting a thermometer 6 in. into the rectum. The thermometer was calibrated against that of the U. S. Bureau of Standards for accuracy and was such that it did not need to be withdrawn from the rectum to be read.† An endotracheal tube with inflatable cuff was inserted, and oxygen consumption was obtained by attachment of this tube to a Benedict-Roth spirometer containing a carbon dioxide absorber.

These preparatory procedures required approximately one hour. After all precooling determinations were made and just before the animal was put into the bath, samples of blood were again taken for sugar, hematocrit, pH, and CO_2 determinations.

All animals were cooled by placing them in a thermostatically controlled water bath at 1 C, where they remained until the rectal temperature was 29.3 ±1 C. After removal from the bath, they were transferred to an 18 C air-conditioned room. For the duration of the experiment the animal's temperature was controlled by adjusting the room temperature. All determinations mentioned were then made at intervals throughout the course of hypothermia. During the period in the bath (Table 1) and shortly thereafter in the cold room, it was necessary in most animals to give intermittent-drop ether anesthesia to control shivering. However, the amount of anesthetic administered was kept at a minimum.

Experiments were terminated by death in 16 of the 20 animals either during hypothermia or during rewarming. Dogs 850, 868, 720, and 784 were maintained hypothermic for a longer time than indicated but were treated during this extended period in an attempt to alter some of the more obvious biochemical changes. This "therapeutic" period is eliminated and will be the subject of a further report. It is emphasized that in all animals, aside from the slow intravenous drip through the cardiac catheter for the first few hours, no fluid or medication was administered.

RESULTS

Temperature.—Animals were removed from the bath at 29.3 ± 1.0 C, and temperatures were permitted to drop to a point where no more anesthetic agent was needed to prevent movement of the animal. This took approximately one to 1½ hours. As the animal's temperature dropped, the room temperature was permitted to rise, so that when the animal reached 23 C the room temperature was 22 C. With a 2 to 4 degree (C) differential in temperature, no trouble was had in maintaining a stable temperature for the duration of the experiment (Table 1). A critical temperature, at which shivering ceased without further anesthetic agent, was found for each dog. For one dog this was 23 C, for another 23.5 C, another 22.5 C., etc. This point was very sharp, and frequently ½ degree above this critical temperature there was movement which ceased only upon the lowering of the temperature the ½ degree. The usual picture of cold narcosis as described with pentobarbital (Nembutal) did not exist at 28 C. It has been our experience to see animals at 23 C lift their heads from the table with eyes open and make purposive movements. Once, however, the above-mentioned critical temperature is encountered, which is usually between 22.5 C and 24.5 C, the temperature remains uniformly constant, varying only slightly as long

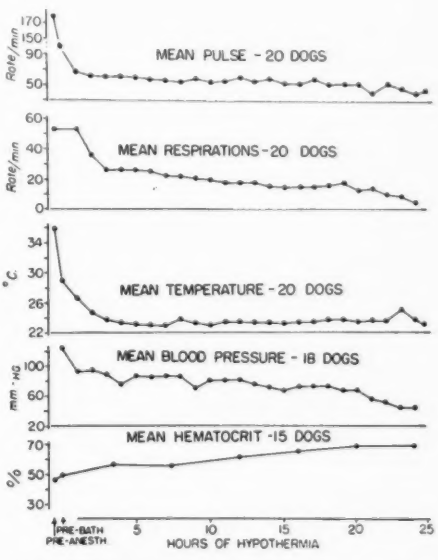


Fig. 1.—Mean hourly values for long-term hypothermic animals.

† Precision Scientific Co., Catalogue No. 031495.

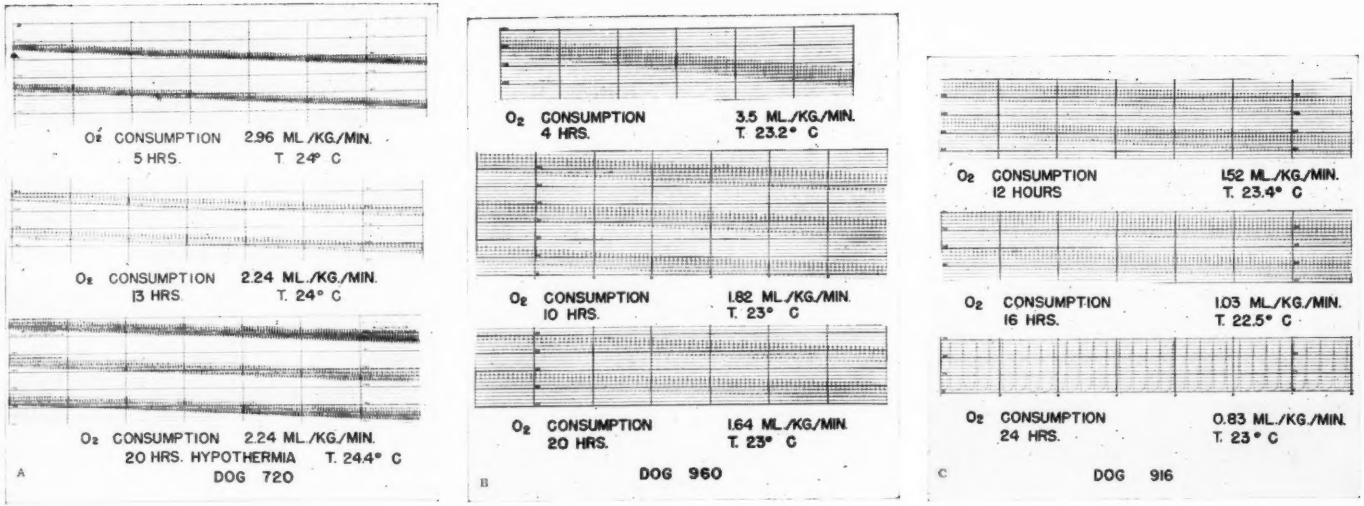


Fig. 2.—*A*, *B*, *C*, and *D*, spirometer tracings during prolonged hypothermia. No positive pressure. Note increase in tidal volume in *C* to maintain minute volume.

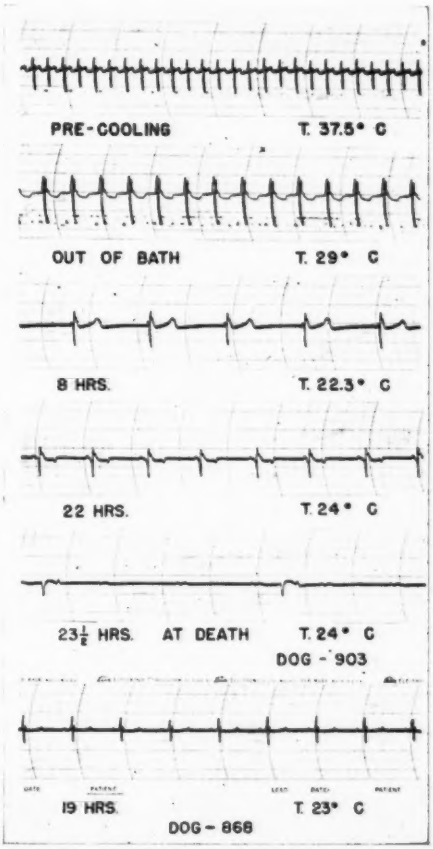
as the ambient temperature is controlled. As may be seen from Figure 1, after the first two hours the mean hourly temperatures for the group varied between 23.5 C and 24.0 C. The irregularity after 22 hours is due to the fact that there were fewer observations made during these hours. The average mean temperature for all animals after the first hour was 23.5 ± .7 C.

Respiration.—As has been so frequently mentioned in hypothermia with pentobarbital anesthesia, when the temperature drops below 28 C it is necessary to resort to positive-pressure respiration because of inadequate respiratory exchange,[13] and certainly at 23 C, unless positive pressure is resorted to,[23] anoxia promptly develops as a result of respiratory failure. In this series, however, not one animal was placed on positive pressure at any time. In Figure 2 are seen four representative spirometer tracings of animals at varying temperatures and times of hypothermia. It may be seen that the tidal exchange is normal and that when respirations do slow there is a compensatory increase in tidal volume so that the minute volume is essentially unchanged (Dog 916 at 24 hours, Fig. 2*C*). Normal respiratory rates and tidal volumes have been seen in animals at 21 C. Although the temperature remained fairly constant during the prolonged hypothermia, the mean respiratory rate for the 20 animals (Fig. 1) was seen to decrease gradually in almost linear fashion from 26 at 5 hours to 15 at 15 hours and then irregularly decline through 24 hours. This decrease, occurring as hypothermia progresses, is not likely due to anesthesia, as no anesthetic is used after the first hour, and, although no blood ether levels were determined, it is doubted if after a few hours an appreciable amount is still present. It is not clear at this time what the reason for the change in pattern of respiration is. With pentobarbital as the precooling anesthetic, this picture is different in that spontaneous respirations usually cease at the lower temperatures. Spurr and co-workers,[15] however, did maintain a series of animals for the most part above 25 C for 10 hours after the use of pentobarbital and report a respiratory rate averaging about seven per minute.

Heart Rate.—As described by others, with the temperature decline there was a decrease in pulse rate. However, during the period of temperature stability (2 to 24 hours), the pulse rate continued to decline gradually (Fig. 1). The mean rate for the first 8 hours was 61, for the second 8 hours 54, and for 16 to 24 hours 48. Minor increases in temperature were accompanied by significant increases in pulse rate.

Examples of the electrocardiographic findings in two of these animals are presented in Figure 3. In general, findings were similar

Fig. 3.—Electrocardiograms in prolonged hypothermia.



to those reported by others in that there was some prolongation of the QRS complex and lengthening of the Q-T interval. However, the findings were variable in most animals. The presence of the "current of injury" (a secondary wave closely following the S wave) has been seen, but not with regularity. Further, as may be seen in Dog 903, although the "current of injury" was present at 8 hours, the animal continued to live for 23½ hours. Osborn [23] reported its occurrence about one-half hour before fibrillation and looked upon it as an ominous sign. This has not been our experience. In this dog the final tracing demonstrates an apparent dissociation between P waves and QRS complex. On the other hand, it was not uncommon to find tracings at 16 and 24 hours of hypothermia like that of Dog 868, i. e., with little change. In general, it may be said that no specific change has occurred in the electrocardiographic tracing with regularity and that it has been of little prognostic importance.

Hematocrit Value.—Numerous investigators have noted the increase in hematocrit value which occurred as the temperature decreased. D'Amato and Hegnauer [24] noted an increase of 15.2% at 20 C, which they ascribed to either an increased red cell volume or a diminution of plasma volume. Ross [25] found an increase of about 10% with cooling during spontaneous respirations. This is similar to the observations of Barbour [26] and of Swan.[3] Alexander,[27] in a report of the Dachau experiments in hypothermia, showed increased red cell counts, which would reflect an increase in hematocrit value.

In this group of experiments there was an increase in hematocrit value in all 15 animals upon which hematocrit values were observed. As shown by McAllister,[28] ether anesthesia in the normal dog may give a rise in hematocrit value. In this series, the hematocrit reading before the anesthetic was started was 48.0 ± 4.7%, and before cooling after almost one hour of ether, 50.2 ± 6.6%. As may be seen from Figure 1, although the temperature remained constant there was generally a continuous increase in the hematocrit reading as time of hypothermia progressed. Examples in six animals are shown in Figure 4. The percentage change of hematocrit value was determined from the last observed hematocrit reading and the prebath reading. For this group the increase was 35 ± 18% (Table 2). Although there was considerable variability, 9 of 15 demonstrated changes of over 30%. Only three showed a change of less than 15%.One animal, Dog 787, showed a hematocrit value of 92 after 17 hours of hypothermia. This determination was repeated several times to verify its accuracy.

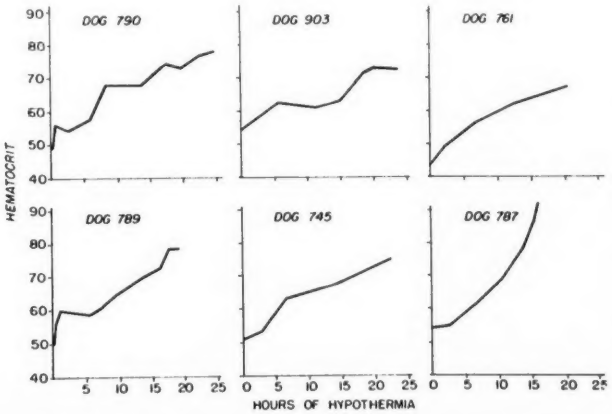


Fig. 4.—Effect of prolonged hypothermia on hematocrit values.

TABLE 2.—*Changes in Hematocrit Value, Plasma Specific Gravity, and Total Plasma Protein During Prolonged Hypothermia*

Dog No.	Hours of Hypothermia	Hematocrit Value, %			Plasma Specific Gravity		Total Protein, Mg. per 100 Cc.		% Change	
		Before Anesthesia	Before Bath	Final	Before Bath	Final	Before Bath	Final	Hematocrit Value	Protein
443	22.0	44	45	52	1,027	1,022	6.9	5.1	15.5	26.0
720	31.5	49	55	69	.....	.....	...	...	32.7	....
745	24.5	..	51	83	.....	.....	...	...	62.7	....
761	21.0	..	49	69	.....	.....	...	...	40.8	....
784	11.5	52	52	73	.....	.....	...	...	40.3	....
787	15.5	..	56	92	.....	.....	...	...	64.2	....
789	20.0	50	58	79	.....	.....	...	...	36.2	....
790	24.0	..	49	79	.....	.....	...	...	61.2	....
850	12.5	..	37	39	1,026	1,018	6.5	3.7	5.4	43.0
903	23.5	..	55	70	1,024	1,015	5.8	2.7	27.2	53.4
906	10.5	..	49	65	1,024	1,020	5.8	4.4	32.6	24.1
916	26.0	46	51	58	1,028	1,016	7.2	3.1	13.7	56.9
931	8.5	41	41	48	1,025	1,023	6.1	5.5	17.0	9.8
960	21.5	52	56	63	1,023	1,017	4.9	3.4	12.5	30.6
968	12.5	51	51	73	1,024	1,021	5.8	4.8	35.2	17.2
Average	19.0	48±4	50±5	67±13	1,025	1,019	6.1±0.7	4.0±1.0	35±18	33±15

In reviewing the protocols of all of these animals, it was found that Animals 443, 850, 903, 906, 916, 931, and 960 had more blood for multiple determinations removed during the experiment. These animals, although showing an increase in hematocrit value, had a lower rise than did those where fewer determinations requiring blood were made. Similarly, dogs with the greatest change in hematocrit value had the least amount of blood withdrawn during the experiment. It would thus seem that the increases in hematocrit value of about 10% seen during the initial cooling become progressively greater as hypothermia continues, unless, perhaps, the animal is bled.

Contraction of the spleen, which has been considered as a possible factor in increasing the hematocrit value, could hardly play a role in this prolonged and progressive increase, thus confirming the findings of Ross [25] that splenectomy does not alter the initial changes seen in hypothermia.

Venous Pressure.—Venous pressures were recorded at frequent intervals in 14 of the 20 animals. All readings were made from the inferior vena cava in the region of the diaphragm. Bigelow,[13] whose determinations were made from the superior vena cava, demonstrated that as long as spontaneous respirations were maintained there was no increase in venous pressure. However, with the advent of positive-pressure artificial respiration the venous pressure gradually rose and continued to do so as the temperature declined, and no record of negative venous pressure was obtained after positive-pressure respiration was instituted. He recorded pressures up to 20 cm. of water and suggested that shivering increased the venous pressure. The latter was likewise the finding of Crismon [29] in rats. Because of the apparent association of high venous pressure with ventricular fibrillation, venesection was suggested by Bigelow. On the other hand, Covino and co-workers [30] reported that central venous pressure was not elevated in hypothermia and that venesection had no influence in reducing ventricular fibrillation.

In 10 of the 14 animals in this series upon which venous pressures were determined there was a decrease in pressure. This may be seen in Figure 5, where venous pressures for five representative animals are presented. Of the four with elevation of venous pressure, the elevation was slight, as is exemplified by Dog 960, shown in the same figure. In none of these four animals were venous pressures as high as those observed by Bigelow. Survival in this latter group was no different from that among animals with decreased venous pressure. Since all animals were breathing spontaneously and were not

shivering, this would affirm Bigelow's findings that as long as spontaneous respirations were maintained there was no increase in venous pressure—even for as long as 26 hours of hypothermia. In fact, in four animals showing lessened venous pressures, as time of hypothermia was extended the decrease became progressively greater (Dogs 868 and 960).

Arterial Blood Pressure.—The results of frequent determination of arterial blood pressure on 18 animals are presented in Figure 1. The observations of Bigelow,[13] Covino,[30] Prec,[31] Hegenauer,[39] and others have been concerned with the effect of progressively decreasing temperature upon the blood pressure. Woodruff [12] presented data on two animals demonstrating the dependence of blood pressure upon temperature.

Our observations on animals maintained at constant temperature for up to 26 hours show an initial drop in blood pressure with cooling, so that by the end of the first hour of hypothermia there was an average decrease in blood pressure of 23% from the precooling level. There was then a progressively steady decline in pressure as the hours of hypothermia progressed. By 8, 16, and 24 hours the mean values for blood pressure were 33%, 44%, and 67%, respectively, less than before cooling.

In general, we have found that the higher the blood pressures before cooling the higher the pressure remained during hypothermia. Blood pressures below 40 mm. Hg were usually prognostic of death within a few hours. However, death occurred as often in animals with more elevated pressures.

Clotting and Prothrombin Times.—Clotting and prothrombin times were determined simultaneously in nine animals before cooling and at intervals during the hypothermic period. Tubes containing blood removed for determinations of clotting time were immediately placed at room temperature. This latter temperature was constant throughout any given experiment. Prothrombin times were determined in a 37.5 C water bath. It is realized that the actual clotting times may be different from that which exists at the temperature of the animal. However, since conditions were kept constant during the experiment, i. e., dog's temperature and room temperature, it would seem that any changes would be due to some alteration of clotting mechanism rather than a direct physical re-

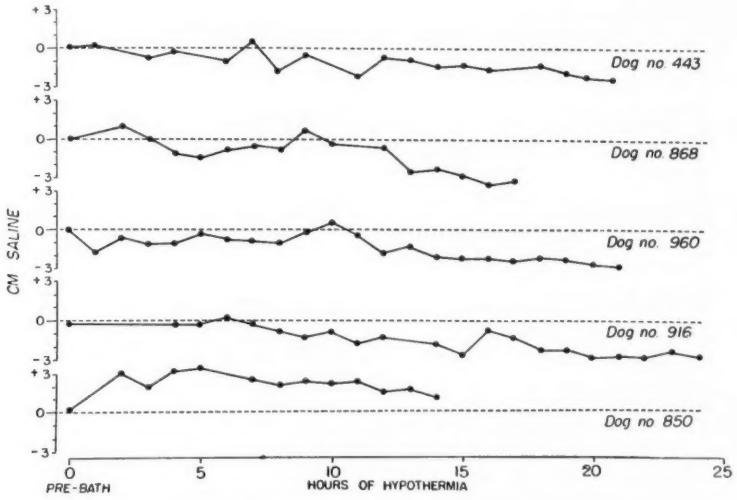


Fig. 5.—Changes of venous pressure in prolonged hypothermia.

sult of cold, as suggested by Ross.[25] Since the animal's temperature was lower than the room temperature, it is possible that clotting time at the animal's temperature would be further prolonged. Changes seen in these values in four representative animals are shown in Figure 6. The alterations in clotting time are present early in hypothermia, and by the fourth hour all animals demonstrated significant increase in coagulation time. Not until six hours, however, did all animals demonstrate an increase in prothrombin time. In all dogs, there was seen at some time during the hypothermia a point at which blood would not clot and it was impossible to determine prothrombin. The time at which this occurred varied from animal to animal. After four hours of hypothermia, coagulation time was more than 70 minutes in Dog 931, and the earliest complete breakdown in prothrombin time was 14 hours in Dog 443.

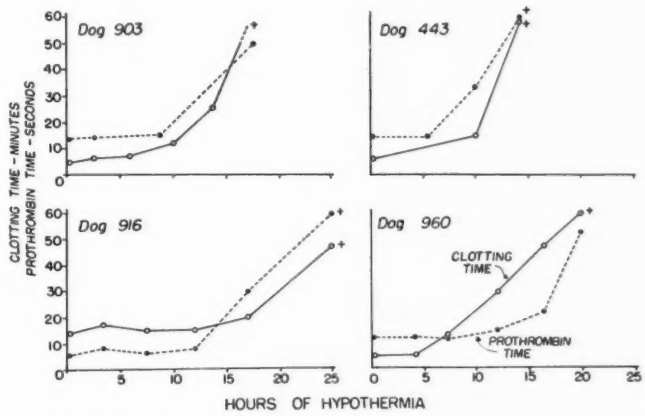


Fig. 6.—Effect of prolonged cooling on clotting and prothrombin times.

Plasma Specific Gravity and Plasma Proteins.—Plasma specific gravity was determined before cooling and at intervals during hypothermia in eight animals. From the specific gravity it was possible to calculate the total plasma protein. This calculated figure agreed within 0.6 mg. per 100 cc. of the actual value for total plasma proteins as determined analytically. In every animal there was a decrease in plasma specific gravity and plasma proteins, the average decrease of proteins for the group being 33±15% (Table 2). In the first few hours of hypothermia, no increase in plasma proteins or specific gravity was observed. The mean (eight animals) prebath 4-, 8-, 12-, 16-, 20-, and 24-hour specific gravities were 1.025, 1.023, 1.022, 1.021, 1.019, 1.019, and 1.018, respectively. Results of albumin and globulin determinations showed a decrease in both. These findings agree with reports that there is little or no change in specific gravity (D'Amato) and of plasma protein (Swan) early in hypothermia. There, however, the similarity ends, for as hypothermia is maintained for many hours the total protein and specific gravity markedly decrease. With the increase in hematocrit value it is to be expected that there is a decrease in total plasma volume due either to capillary leakage or to differential plasma trapping, as suggested by some. There is no apparent explanation at present which is compatible with all findings for the decreased plasma specific gravity and total protein.

Blood Sugar.—Because of the reported variable response of blood sugar to short-term hypothermia, observations were made at intervals on 10 of the prolonged hypothermic animals and are presented in Table 3. As has been reported by Brewster,[32] there was an increase in blood sugar during ether anes-

TABLE 3.—*Effect of Prolonged Hypothermia on the Blood Sugar*

Dog No.	Hours of Hypothermia*	Blood Sugar, Mg. per 100 Cc. Before Ether	Before Bath	Final	Per Cent Decrease†
720	28	77	100	38	62
787	15	62	141	48	65
789	15	72	147	23	84
790	24	63	130	68	48
850	12	..	139	55	60
868	18	..	129	25	81
903	23	65	110	44	60
906	10	73	114	81	20
916	25	91	118	3	97
960	21	76	146	76	48
Average	19	72	127	46	63±18

* Time of last sugar sample.
† Comparison of before bath and final samples.

thesia. The average blood sugar value before anesthesia was 72 mg. per 100 cc., and after approximately one hour of ether it was 127 mg. per 100 cc. In these animals the mean terminal blood sugar value was 46 mg. per 100 cc., a decrease of 63±18% for an average of 19 hours of hypothermia. Four animals (Fig. 7) represent the patterns followed by all animals. Urine samples collected throughout the period of hypothermia in all animals showed 4+ qualitative sugar values. Unfortunately, when severe hypoglycemic levels were reached the urine had

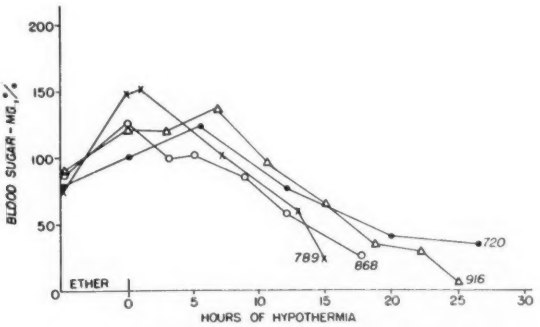


Fig. 7.—Effect of prolonged cooling on blood sugar.

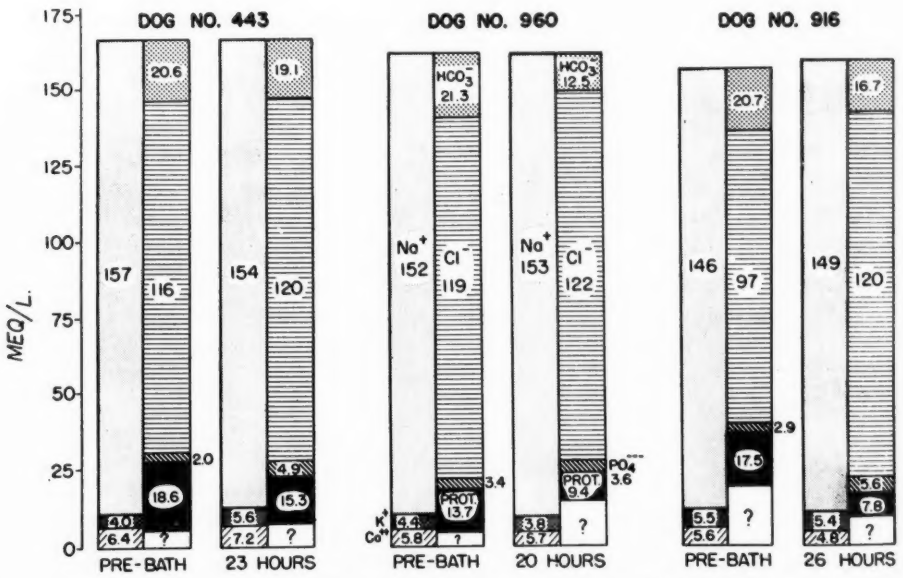


Fig. 8.—Electrolyte changes in three animals with prolonged hypothermia.

already ceased flowing for several hours; hence it was impossible to say that sugar was being lost via the kidneys in the presence of low blood sugar levels. Studies are in progress to evaluate whether it is inability to mobilize sugar or actual depletion of liver glycogen which leads to the low blood levels.

Electrolytes. — The typical electrolyte changes in prolonged hypothermia are depicted by Figure 8, where the findings of three animals maintained hypothermic for 26, 23, and 20 hours are presented.

Serum sodium: The average value for sodium in 12 dogs before cooling was 150±3.5 mEq/L., while the terminal samples taken had an average of 148±6.8 mEq/L. These findings are in keeping with those reported by Swan [33] of short-term hypothermia and by Talbott [11] of a patient with prolonged hypothermia (temperature always above 78.8 F [26 C]). No significant change in serum sodium was seen in any animal.

Serum Calcium: Bigelow [13] found a variable effect upon serum calcium when dogs were cooled, and Elliott and Crismon [34] reported a rise when rats were made hypothermic. In nine animals in our series the prebath average was 5.6±0.42 mEq/L. and the final determination was 5.3±0.85 mEq/L. There were no significant changes observed during the course of prolonged hypothermia.

Serum Potassium: Estimations of potassium at intervals during prolonged hypothermia in nine dogs were of interest, in view of the differences found in the literature for short-term cooling. The prebath average was 4.7±0.5 mEq/L., and the terminal average, 4.0±1.3 mEq/L. Although no statistically significant difference exists between the initial and the final determinations, our results are not in total disagreement with those of others. While Bigelow [13] reported a rise in serum potassium in dogs breathing a mixture of 5% carbon dioxide in 95% oxygen and Elliott and Crismon [34] showed a rise in cooled rats, Swan [33] found a fall in his hypothermic dogs, as did Ross.[25] The latter felt that, although there was a trend toward a decrease, the results were indefinite. It was also suggested that the fall may have been greater in those animals on mechanical respiration than in those breathing spontaneously. It is to be emphasized that all these references concerned animals hypothermic for short periods. Our results for potassium within the first few hours of cooling tend to agree with those of Swan. There was a significant decrease in plasma potassium in eight of nine animals. As cooling progressed, however, there was a tendency toward a return to precooling plasma levels. Although these animals were not hyperventilated artificially at any time, respiratory rates were greater in the first few hours than terminally; hence, as Swan and Ross have suggested, there may be a relationship between potassium and respiration. On the other hand, the decrease in potassium seen may be the result of ether anesthesia. That this anesthetic agent may result in a fall of serum potassium of 0.5 to 1.5 mEq/L. was shown by Fay.[35] It has been impossible in these experiments to correlate the changes of potassium with either the plasma level of CO_2 or the pH of blood. It is of interest to note that Swan could not account for the decreased blood potassium by a commensurate loss in the urine. Although balance studies were not done in these experiments, it appeared that potassium levels tended to rise after cessation of urinary flow.

Chlorides and Phosphate: There was an increase in chlorides of 7% in nine animals observed. The precooling chlorides were 110±6 mEq/L., and the mean final readings were 118±5 mEq/L. These were the findings of Swan [33] for short-term hypothermic animals. Woodruff [12] showed no significant change in four animals observed, the longest for seven and one-quarter hours.

The serum phosphorus in seven animals was 2.82±0.61 mEq/L. before cooling and 3.60±1.44 mEq/L. terminally. This represents a 28% increase during the cooling period. The increase was noted in all animals, and, as might be expected, this did not become significant until after urine flow had ceased. In hypothermia of short term,

Swan [33] demonstrated a general decrease and Fleming,[36] no change in this anion.

Acid-Base Balance.—Simultaneous plasma CO_2 and pH were determined in 10 animals at intervals of hypothermia. The pCO_2 was obtained from the nomogram of Singer and Hastings.[37] Results of four animals, Dogs 903, 960, 916, and 443, depicting the variations observed are seen in Figure 9. These dogs all survived more than 20 hours of hypothermia.

Before Cooling: Eight of ten animals had a blood pH of over 7.4 when the preliminary blood samples were taken, i. e., before anesthesia or cooling. This was due to the hyperventilation of the animal which occurred when it was restrained. The mean pH at this time was 7.52±0.27. After anesthesia and preliminary to being placed in the bath, the pH was 7.47±0.23. Although all animals displayed some drop in pH, only in two dogs was this precipitous and below pH 7.4. The pH declined in Dog 960 from 7.71 to 6.98 and in Dog 949 from 7.50 to 7.15. Plasma CO_2 changed in similar fashion, there being a decrease in all animals during anesthesia. The mean CO_2 was 22.2±2.2 mEq/L. before anesthesia and 16.0±2.7 mEq/L. before cooling. In all animals, except Dog 960, the pCO_2 remained about 20 mm. of Hg.

These are typical of the findings of Brewster [32] for the effect of ether anesthesia on the dog. They demonstrate in general a metabolic acidosis which Brewster speculates upon as being due to excessive epinephrine secretion with mobilization of liver and muscle glycogen to form glucose and lactic acid. This series of animals thus was introduced to cooling when they had decreased plasma CO_2. This is contrary to the

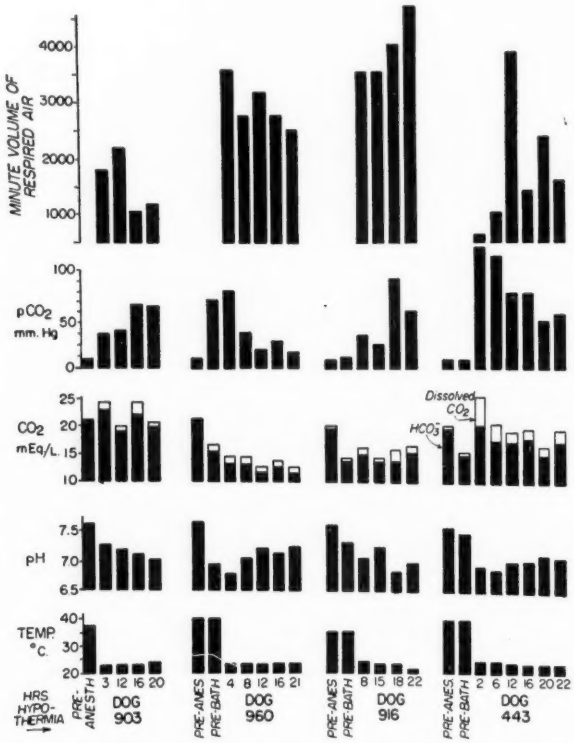


Fig. 9.—Acid-base balance in prolonged hypothermia.

recommendation of Osborn [23] that induction of respiratory acidosis, with an increased plasma CO_2, for an hour before cooling has a beneficial effect.

During Prolonged Cooling: Of all the observations, these proved most interesting, because it was here that the greatest differences between the use of ether and pentobarbital anesthesia were apparent. It is felt that the changes occurring after the first few hours are due to hypothermia alone and not to a combination of hypothermia and anesthesia. It can be demonstrated that the animal has not lost completely its ability to compensate for acid-base changes and that the minute respiratory volume at low temperatures may be greater than normal without the use of positive-pressure respiration. In most animals (Dogs 960 and 916; Fig. 9, for example), there was a significant drop in pH during the early hours of hypothermia accompanied by a decrease in CO_2. Slight increase in pCO_2 occurred, indicating that the acidosis, although predominantly metabolic, had some respiratory component. By the maintenance of a large minute volume of respired air, the pCO_2 was kept below normal (Dog 960) or at normal (Dog 916). This was in the presence of a low pH and a decreased CO_2 value, indicating that acidosis was metabolic in type during prolonged hypothermia. However, in only one animal (Dog 960) was there a significant lowering of bicarbonate below the precooling level; consequently it is difficult to say that the metabolic acidosis was progressive over that seen as a result of the ether. Dog 903 is an example of an animal whose minute volume became depressed after 14 hours of hypothermia, and as a result there was an increase in pCO_2 from low-normal to just above normal limits. The pH continued to fall, and the CO_2 was at normal levels, suggesting a slight respiratory component of the metabolic acidosis.

Dog 443 demonstrates conclusively the great ability of the animal to regulate its own minute respiratory volume even after many hours of hypothermia. This animal had the usual precooling response to anesthesia, going into the bath with a respiratory alkalosis. For the first six hours of cooling the animal was rebreathing CO_2 because the CO_2 absorber in the spirometer through which it was breathing for long periods was contaminated. By the time this was discovered, a typical respiratory acidosis with pCO_2 of 120 mm. Hg was present. When the situation was discovered and the animal was permitted to breathe freely and blow off CO_2, there was a great increase in minute volume with a drop in CO_2 and pCO_2 and some increase in pH of the blood. By the 20th hour, the pCO_2 was normal and the picture was that of a metabolic acidosis, as seen in the other animals. During this prolonged period the temperature was stable at 23 C.

From the observations of acid-base balance under the conditions of these experiments, certain conclusions might be made and impressions conjectured upon. It is doubtful that the low pH per se without rapid change is of such serious import as suggested by Swan. It was not infrequent to see pH's of 6.8 to 7.0 for several hours and to have the animal continue hypothermic for long periods of time. It was our distinct impression that there was no relationship between the pH and the death of the animal due to fibrillation. In practically all instances where there was an increase in CO_2 there was a commensurate increase in bicarbonate. This again demonstrates that all of the compensatory ability is not lost even after many hours of cooling, for by increase of the bicarbonate there is permitted an increased concentration of H_2CO_3 without as great a depression of pH as would otherwise occur. It would seem that without associated respiratory depression of anesthesia these animals can do just about as well on spontaneous breathing as with vigorous positive pressure.

COMMENT

The use of pentobarbital sodium for practically all experimentation in hypothermia is hard to explain. It is most difficult to assess whether the narcotic effects of cold replace or augment the barbiturate effect. Certainly it must be questioned, at least in many of

the short-term hypothermia observations, whether or not this agent has been metabolized, so that the changes of hypothermia alone are being studied. This is doubted, in view of the relatively large amount of anesthetic required to prevent shivering and the general depression of metabolic activity produced by the hypothermia. Much of the respiratory depression observed when pentobarbital sodium is used must be due to it, for with ether anesthesia, as described, the picture is different. Bigelow has also indicated that with vinyl ether spontaneous respiration did not cease until 22 C. Ross commented that O_2 consumption was higher with ether than when barbiturates were used. That this may not be so is seen from the following.

It has been found in this laboratory that oxygen consumption for 20 normothermic animals under barbiturate anesthesia was 7.0 ± 1.1 ml/kg/min. At the end of one hour of hypothermia with the mean temperature 26.4 C, the mean oxygen consumption for the group of animals presented in the study was 2.18 ml/kg/min., or 31% of normal. These findings are in keeping with the report of Hegnauer and D'Amato [38] on oxygen consumption in hypothermia using pentobarbital anesthesia. This data will be elaborated upon in a subsequent report.

Recently Covino and others [30] concluded that cardiac arrhythmias and ventricular fibrillation occurred more frequently in dogs under pentobarbital than in those under thiopental sodium or ether anesthesia. It was felt that perhaps the myocardial depressant effect of ether was responsible for the better showing of etherized animals. Although in this study there has been no attempt to relate the anesthetic agent to ventricular fibrillation, it is of interest to note that animals had catheters in their hearts for the duration of the experiment without the deleterious effect recorded by Hegnauer.[39] On occasion during the hypothermia, these catheters were readjusted under fluoroscopy.

Unfortunately, as has been shown, ether, even though rapidly eliminated from the body, produces changes in itself which may well reflect upon the subsequent observations. Certainly it must be felt that the drop in pH and decrease in the HCO^- are not wholly desirable. On the other hand, one might conjecture from the findings that perhaps too much emphasis has been placed on the importance of the maintenance of these levels during hypothermia and that there may be a relatively wide range of safety in blood pH, for example, here as in the normal animal. It must be noted that this effect of ether anesthesia in dogs has not been observed in adult humans [40] but has in infants and children.[41] As already stated, under the condition of these experiments there appeared to be no relationship between ventricular fibrillation and blood pH, plasma CO_2, potassium, venous pressure, hematocrit value, or the other observations, except for the blood pressure and temperature. A drop of blood pressure below 40 mm. Hg was almost always prognostic of death within a short time. In regard to temperature, it may be parenthetically stated that in this laboratory, under the conditions outlined, it was impossible to keep animals alive with any regularity below 22 C, either in the early periods of hypothermia or after many hours. This was in spite of finding the results of all observations unchanged from those at 23 C, where survival was greater.

It must be concluded from these studies that prolonged hypothermia in the temperature range of 22 to 24 C, where oxygen consumption is 15% to 20% of normal, is not akin to a state of hibernation or relative physiological inactivity, for, although the temperature may remain stable, practically all observations reported upon show changes which become progressively greater with the length of hypothermia. The complete abolition of the clotting mechanism is but one example of the complex metabolic alterations resulting. There is reason to believe that many enzyme systems are interferred with as hypothermia ‡ is prolonged, and it remains to be proved whether such changes are only temporary. In spite of the fact that hypothermia has been used with

‡ Fisher, B., and Fedor, E.: Unpublished data.

relative safety in some patients, it still must be considered as an experimental method, and it is hoped that studies such as this will, instead of creating confusion, tend to point out the problems still remaining to be solved concerning this modality. Certainly it would seem important to know whether six or eight hours at 24 C are as innocuous as two or three. Results reported here, and to be presented, suggest that this may not be so and that the longer hypothermia exists the more complex and pronounced are the changes from the normal and possibly the more difficult it becomes to correct them.

SUMMARY

Observations made on 20 dogs maintained for 6.5 to 31.5 hours at a mean temperature of 23.5±0.7 C with use of ether as the anesthetic agent to control shivering are reported. The body temperature could be maintained by adjusting the ambient temperature. Each dog had its own critical temperature, at which point no further ether was needed to control shivering.

No need was found for positive-pressure respiration down to temperatures of 21 C, and during the prolonged hypothermia animals maintained their respiratory minute volumes.

Changes in pulse, blood pressure, venous pressure, and hematocrit values are described.

Gradual prolongation of clotting and prothrombin times occurs, in the early hours of hypothermia, followed by a percipitous deterioration of these mechanisms.

Significant decreases in plasma specific gravity and plasma proteins are seen.

Progressive hypoglycemia occurs with prolongation of cooling.

Observations of serum sodium, calcium, potassium, chlorides, and phosphate demonstrate marked changes in some of the ions and not in others.

Changes in acid-base balance are discussed, and it is demonstrated that even after many hours of hypothermia at low temperatures the animal has not completely lost its ability to compensate for these alterations.

It is believed that the more prolonged the hypothermia the more complex are the physiologic alterations and perhaps the more difficult it may be to restore them to normal.

The Department of Research Medicine, Dr. T. S. Danowski, Director, did the electrolyte determinations, and Morton Levine, John Black, and Robert Fine gave technical assistance.

DISCUSSION

Dr. John H. Grindlay, Rochester, Minn.: Although hypothermia is not yet a common adjuvant in surgery, it may at some time in the future be a more commonly employed one, at least in procedures such as repair of aneurysms in the circle of Willis, in cardiac surgery, or during other procedures of vascular surgery.

I should like to mention a point that Dr. Fisher has not had time to mention. It is surprising that a greater blood level of ether is required to keep an animal at a constant level of anesthesia (a constant level as determined by the electroencephalogram) as the temperature of the animal gets lower than is required when the temperature is that of the animal normally.

It surprised my colleague, Dr. Albert Faulconer, that ether concentrations of the blood in animals at low temperatures were greater while the animal was kept at the same level of anesthesia at low body temperature than the concentration when the animal was at its normal temperature.

Dr. Edward M. Kent, Pittsburgh: All of us interested in hypothermia as a clinical weapon or as a research tool agree that a great deal of laboratory research is necessary. Dr. Fisher's work is a carefully prepared step in that direction, and therefore the contribution is a valuable one.

A notable observation has been the finding that when ether was employed as a precooling anesthetic agent spontaneous respiratory function continued in all of his animals and that it was not necessary to resort to positive-pressure techniques or artificial respiratory assistance. This appears to have been due to an absence of central respiratory depression.

There is also some suspicion that the commonly employed barbiturates may exert some degree of myocardial depression. If this is so, it is possible that the absence of such an effect may have favorably altered the cardiac function in a significant way for this study.

Dr. Fisher conjectures, as a result of his findings, that a lowered pH which is not followed by precipitous increase may not be of importance, as suggested by Swan. In this regard it is my understanding that this possibility was merely proposed by Swan and his associates as the result of observations made on a single hypothermic dog which

developed ventricular fibrillation in the presence of lowered pH at a point of investigation before circulatory occlusion and cardiotomy had been carried out.

In general, the experiments of Swan which provided the information on the role of pH and other matters were made upon cooled dogs which were subjected to thoracotomy, circulatory occlusion for 15 minutes, and auricular cardiotomy. None of these conditions pertained in the animals used by Dr. Fisher.

The findings presented today suggest that the longer hypothermia exists the more complex and more pronounced are the changes from the normal and, possibly, the more difficult it becomes to correct them. These observations and many more like them are of great importance to us. In general, Dr. Fisher found that his dogs for the most part would not survive cooling at a level of 22 C to 24 C for a period as long as 24 hours.

Since hypothermia is capable of reducing metabolism and of producing a so-called physiologic hypotension, the method has been proposed as a source of possible clinical value in the management of a variety of conditions. As Dr. Fisher has said, Dr. Swan outlined a potential group of such circumstances, and they include the reduction of oxygen need under reversible circumstances, such as in pulmonary embolism, including the potential use for certain surgical procedures or for reducing internal hemorrhage, to reduce oxygen need and establish hypotension in the management of such problems as myocardial infarction, and to combat hyperpyrexia as manifested in heat stroke or due to thyrotoxicosis, for example.

Dr. Swan has properly emphasized the necessity for and the magnitude of the problems which must be answered by laboratory research before body cooling can safely be employed in these ways.

Dr. Swan has been in attendance at this meeting. I do not know whether he is here this afternoon, but if he is I am certain that all of us would benefit by his discussion of Dr. Fisher's paper.

Dr. Henry Swan, Denver: I do not want to be identified as being a person who thinks only in the cold, and therefore I had not intended to discuss this very fine paper. I really do not have much to contribute to it, because the work that I have listened to here I consider, as far as I know, to be the first of what I hope will be a large number of careful studies of hypothermia under prolonged conditions.

We have limited our work entirely to what one might call acute hypothermia. I have always been scared to death of it. My philosophy has been that I do not know what is going on; I have some very definite purposes for it, and I would like to induce it and get the job done and get the patient back up where I believe I can understand him a little better, as quickly as possible.

This is a purely emotional approach, as you can see. There is no good reason that I know of to desire to cool rapidly or to warm rapidly or, until this afternoon, to worry about how long the temperature of the patient or the animal is down. Consequently, we have had no real experience with prolonged hypothermia either in the laboratory or in the human.

I think the longest human case we had was a patient who was operated on for an aortic lesion, and the total duration of the operation was 12 hours. The patient did well and showed no particular harmful effects from hypothermia of that duration.

In regard to Dr. Grindlay's comment, this particular patient went for 12 hours on a quarter of a can of ether, and we used no ether at all for a period of 8 hours. Therefore, I am rather surprised to hear Dr. Grindlay's comment about the consumption of ether.

I think Dr. Fisher and his group are to be very much complimented on this work they are doing. They are approaching a very important problem in a careful way. My only comment here is that as we have gone on in hypothermia I believe it is true, as Dr. Fisher indicated, that we are not always studying the same things. Reports that are coming out from various laboratories are beginning to emphasize the fact that there are a lot of variables in the experimental techniques which one did not suspect beforehand.

Dr. Fisher emphasized anesthesia. I will certainly agree with that. A dog in our laboratory rarely survives with unsupported respiration if pentobarbital (Nembutal) anesthesia is used. The respiration goes down very low; the animal becomes severely hypoxic and acidotic and goes into ventricular fibrillation very early.

Attempting the use chloralose, with the understanding that this agent does not suppress respiration, we got results in the unrespired animal which were not much better. We can get by at 30 C, but at 25 C again we have difficulty. We have been able to get along with ether down to 22 C and have the animals get through the first 10 or 15 hours of hypothermia, which is very important.

Here, then, is the matter of what type of anesthesia you are going to use—what pharmacologic agent is involved. Also, the matter of supporting respiration is of tremendous importance, and what happens to the cardiovascular system, what happens to the glucose metabolism, and what happens to the myocardial function, I believe, may be quite different in animals that have had supported respiration as contrasted to animals that have not had supported respiration and in whom I believe hypoxia may occur.

Consequently it is becoming increasingly apparent that one must define these variables and separate them out and study what they mean, and then, I believe, when this is done, part of the apparent confusion and the conflicting reports which are coming from various laboratories probably will start to straighten out and will start to fit back into a picture again.

DR. BERNARD FISHER, Pittsburgh: I should like to thank Drs. Grindlay, Kent, and Swan for their comments.

Certainly we could not include in this ten-minute discussion everything that will be included in the published paper, but we agree with Dr. Swan that we hope the purpose of this paper is not to add confusion to the problem but to point out some of the variables that do exist.

We are interested also in Dr. Grindlay's comment about the use of ether, because in our experience after the first hour of hypothermia we have to give these animals no ether whatsoever, provided we get them to the critical temperature which was mentioned in the paper.

DR. JOHN H. GRINDLAY: Before there is further misunderstanding, I would like to repeat what I said—that the concentration of ether in the blood becomes higher as temperature decreases during hypothermia.

REFERENCES

1. McQuiston, W. D.: Anesthetic Problems in Cardiac Surgery in Children, Anesthesiology **10**: 590, 1949.

2. Bailey, C. P.; Cookson, B. A.; Downing, D. F., and Neptune, W. B.: Cardiac Surgery Under Hypothermia, J. Thoracic Surg. **27**:73, 1954.

3. Swan, H.; Zeavin, I.; Blount, S. G., Jr., and Virtue, R. W.: Surgery by Direct Vision in the Open Heart During Hypothermia, J. A. M. A. **153**:1081, 1953.

4. Lewis, F. J., and Taufic, M.: Closure of Atrial Septal Defects with the Aid of Hypothermia, Surgery **77**:199, 1949.

5. DeCourcy, C. B., and DeCourcy, J. L.: Hypothermia in Hyperthyroidism, Am. J. Surg. **77**:199, 1949.

6. Woringer, E.; Schneider, J.; Baumgartner, J., and Thomalske, G.: Essai critique sur l'effet de l'hibernation artificial sur 19 cas de souffrances du tronc cérébral après traumatisme sélectionnés pour leur gravité parmi 270 comas post-commotionnels, Anesth. et analg. **11**:34, 1954.

7. Swan, H.: The Current Status of Hypothermia, Editorial, A. M. A. Arch. Surg. **69**:597, 1954.

8. Smith, L. W., and Fay, T.: Temperature Factors in Cancer and Embryonal Cell Growth, J. A. M. A. **113**:653, 1939.

9. Fay, T.: Observations on Prolonged Human Refrigeration, New York J. Med. **40**:1351, 1940.

10. Dill, D. B., and Forbes, W. H.: Respiratory and Metabolic Effects of Hypothermia, Am. J. Physiol. **132**:685, 1941.

11. Talbott, J. H.; Consolazio, W. V., and Pecora, L. J.: Hypothermia, Arch. Int. Med. **168**:1120, 1941.

12. Woodruff, L. M.: Survival of Hypothermia by the Dog, Anesthesiology **2**:410, 1941.

13. Bigelow, W. G.; Lindsay, W. K., and Greenwood, W. F.: Hypothermia—Its Possible Role in Cardiac Surgery, Ann. Surg. **132**:849, 1950.

14. Spurr, G. B.; Hutt, B. K., and Horvath, S. M.: Prolonged Hypothermia in the Dog, Am. J. Physiol. **178**:275, 1954.

15. Spurr, G. B.; Hutt, B. K., and Horvath, S. M.: Responses of Dogs to Hypothermia, Am. J. Physiol. **179**:139, 1954.

16. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, Bull. U. S. Army M. Dept. (No. 71) p. 66, 1943.

17. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, Vol. 2, Methods.

18. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475, 1921.

19. Fiske, C. H., and Subbarrow, Y.: The Calorometric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

20. Majoor, C. L. H.: The Possibility of Detecting Individual Proteins in Blood Serum by Differentiation of Solubility Curves in Concentrated Sodium Sulfate Solutions, Yale J. Biol. & Med. **18**:419, 1945-1946.

21. Milne, J.: Serum Protein Fractionation: A Comparison of Sodium Sulfate Precipitation and Electrophoresis, J. Biol. Chem. **169**:595, 1947.

22. Nelson, N.: A Photometric Adaptation of the Somogyi Method for the Determination of Glucose, J. Biol. Chem. **153**:375, 1944.

23. Osborn, J. J.: Experimental Hypothermia: Respiratory and Blood pH Changes in Relation to Cardiac Function, Am. J. Physiol. **175**:389, 1953.

24. D'Amato, H. E., and Hegnauer, A. H.: Blood Volume in the Hypothermic Dog, Am. J. Physiol. **173**:100, 1953.

25. Ross, D. N.: Physiologic Observations During Hypothermia, Guy's Hosp. Rep. **103**:116, 1954.

26. Barbour, H. G.; McKay, E. A., and Griffith, W. P.: Water Shifts in Deep Hypothermia, Am. J. Physiol. **140**:9, 1943.

27. Alexander, L.: Treatment of Shock from Prolonged Exposure to Cold, Especially in Water, Report No. 250, Office of Publication Board, Department of Commerce, Washington, D. C., 1946.

28. McAllister, N. N.: The Effect of Ether Anesthesia on the Volume of Plasma and Extracellular Fluid, Am. J. Physiol. **124**:391, 1938.

29. Crismon, J. M.: Effect of Hypothermia on the Heart Rate, the Arterial Pulse, and the Electrocardiogram of the Rat, Arch. Int. Med. **74**:235, 1944.

30. Covino, B. G.; Charleson, D. A., and D'Amato, H. E.: Ventricular Fibrillation in the Hypothermic Dog, Am. J. Physiol. **178**:148, 1954.

31. Prec, O.; Rosenman, R.; Braun, K.; Robard, S., and Katz, L. N.: The Cardiovascular Effect of Acutely Induced Hypothermia, J. Clin. Invest. **28**:293, 1949.

32. Brewster, W. R., Jr.; Bunker, J. P., and Beecher, H. K.: Metabolic Effects of Anesthesia: VI. Mechanism of Metabolic Acidosis and Hyperglycemia During Ether Anesthesia in the Dog, Am. J. Physiol. **171**:37, 1952.

33. Swan, H.; Zeavin, I.; Holmes, J. H., and Montgomery, V.: Cessation of Circulation in General Hypothermia: I. Physiologic Changes and Their Control, Ann. Surg. **138**:360, 1953.

34. Elliott, H. W., and Crismon, J. M.: Increased Sensitivity of Hypothermic Rats and Injected Potassium and the Influence of Calcium, Digitalis, and Glucose on Survival, Am. J. Physiol. **151**:366, 1947.

35. Fay, M. M.; Andersch, M., and Kenyon, M. B.: Blood Studies Under Anesthesia, J. Pharmacol. & Exper. Therap. **66**:224, 1939.

36. Fleming, R.: Acid-Base Balance of the Blood in Dogs at Reduced Body Temperature, A. M. A. Arch. Surg. **68**:145, 1954.

37. Singer, R. B., and Hastings, A. B.: An Improved Clinical Method for the Estimation of Disturbances of the Acid-Base Balance of Human Blood, Medicine **27**:223, 1948.

38. Hegnauer, A. H., and D'Amato, H. E.: Oxygen Consumption and Cardiac Output in the Hypothermic Dog, Am. J. Physiol. **178**:138, 1954.

39. Hegnauer, A. H., and D'Amato, H. E.: Influence of Intraventricular Catheters on the Course of Immersion Hypothermia in the Dog, Am. J. Physiol. **167**:63, 1951.

40. Beecher, H. K.; Francis, L., and Anfinsen, C. B.: Metabolic Effects of Anesthesia in Man, J. Pharmacol. & Exper. Therap. **98**:38, 1950.

41. Bunker, J. P.; Brewster, W. R.; Smith, R. M., and Beecher, H. K.: Metabolic Effects of Anesthesia in Man: III. Acid Base Balance in Infants and Children During Anesthesia, J. Appl. Physiol. **5**:233, 1952.

Pliable Plastic Aortic Grafts

Experimental Comparison of a Number of Materials

EDMUND J. HARRIS, M.D.
HARRIS B. SHUMACKER JR., M.D.
HARRY SIDERYS, M.D.
THOMAS C. MOORE, M.D.
and
PAUL F. GRICE, M.D., Indianapolis

The search for the ideal plastic material for use as an arterial substitute is important in view of the fact that autogenous and homologous vascular grafts are not available in quantities sufficient to meet the demand. Autogenous vein grafts are suitable for reconstruction of peripheral arteries but not for bridging defects of the aorta or its bifurcation. By and large, arterial homografts have proved eminently satisfactory in human cases during a period of observation extending over a number of years. It is known that these homografts do not survive as living structures but serve as a scaffolding for the ingrowth of tissue from the host. It is also known from experimental studies that degenerative changes, such as calcification, fragmentation of the elastic tissue, and aneurysmal dilatation, take place with the passage of time. To be sure, most of the reported studies concern homografts preserved by some method other than the freeze-drying technique, which is currently most widely used, and perhaps such changes occur less commonly with freeze-dried homografts. Though experiences with homologous grafting in patients have not been entirely free of such difficulties, they have been good on the whole. At the present time, the greatest disadvantage of the homograft is the difficulty of its procurement and preparation.

Effective plastic arterial substitutes should be readily available, easily constructed to meet various demands of size and shape, sterilizable by common operating room methods, easily affixable to the ends of the blood vessels by ordinary vascular suture techniques, nonreactive and "hemorepellent," essentially impervious to blood, and readily incorporated in the newly formed vessel laid down by the host. Ideally, they should be capable of being used satisfactorily for smaller arteries, as well as for the aorta, and should conform to the bends and creases of the body without wrinkling.

The initial impetus to the study of plastic substitutes came from the work of Voorhees, Jaretzki, and Blakemore,[1] who demonstrated that tubes made of Vinyon-N cloth could serve satisfactorily as aortic prostheses in dogs. The first experiments in our laboratory were with a thin nylon cloth which had been used with satisfaction in the closure of cardiac septal defects. Because of the initial considerable loss of blood through the graft wall, it was felt advantageous to render the fabric impervious to blood. This was accomplished by heat fusion with polyethylene (Polythene). The preliminary studies gave encouraging results in animals,[2] and the grafts made of this material were used successfully in human cases.[3] It was obvious, however, that more suitable plastic prostheses might be discovered. It is the purpose of this report to compare a number of plastic materials used as aortic prostheses with freeze-dried homografts.

MATERIALS AND METHODS

Five types of grafts were used. The arterial homografts were freeze-dried in the usual manner.

Submitted for publication April 25, 1955.

From the Department of Surgery, Indiana University Medical Center. Aided by a contract between the Office of Naval Research, the United States Navy, and Indiana University and by grants from the James Whitcomb Riley Memorial Association and the Indiana Heart Association.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

The aortas were removed without aseptic precautions, cleaned of all fatty areolar tissue, covered with liquid ethylene oxide for one hour, frozen in Pyrex tubes in dry ice-acetone baths, lyophilized, and stored in sealed tubes filled with nitrogen. They were reconstituted by immersion for one hour in warm isotonic saline solution containing streptomycin and penicillin.

The second type of aortic graft was made of nylon filter fabric (Fig. 1).* This fabric is designated as an off-balance taffeta, being constructed of multifilament highly twisted yarn strands with a warp count of 232 and a filling count of 96. The apertures in the cloth occur between the compact adjacent yarn strands. The yarn is 70 denier high-tenacity nylon with 35 turns per square inch in length. After autoclaving, the fabric has such a resistance that a pressure equivalent to from 4 to 5 in. of water will cause it to pass 20 c. f. m. per square foot of air. The tubular grafts were constructed with the direction of the strands of the warp at a 45-degree angle to the long axis of the graft.

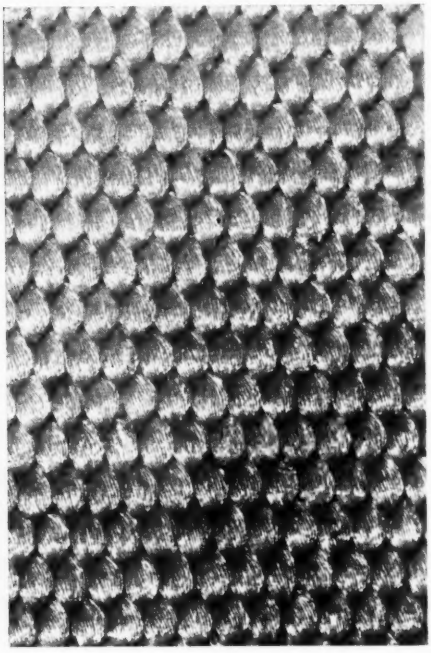


Fig. 1.—Low power magnification (× 25) of nylon filter fabric showing general character of weave.

The material for the third type of graft was prepared by fusing a thin film of polyethylene† between two sheets of finely woven nylon,‡ as previously described.[2] A single layer of the same nylon fabric and polyethylene film were fused together commercially by impulse sealing.§ From this material the fourth type of graft was made. The fifth was made of Vinyon-N cloth, like that used by Voorhees, Jaretzki, and Blakemore.‖

All of the plastic grafts were made by sewing together the sides of the folded cloth with a sewing machine, using a fine needle and fine nylon thread placed 25 stitches per inch. The grafts were 2.5 cm. in circumference (0.78 cm. in diameter) and 5.4 cm. in length. None of the plastic materials or the finished grafts were washed. The Vinyon-N grafts were sterilized by boiling in water for 15 minutes, and the remainder, by autoclaving for 10 minutes at 250 F and at 20 lb. of pressure.

Healthy mongrel dogs ranging in weight from 11 to 17 kg., were used. They were anesthetized with intravenously administered thiopental sodium, supplemented with an ether-oxygen mixture delivered through an endotracheal tube by means of an intermittent positive pressure apparatus. To prevent ischemic paralysis from prolonged occlusion of the thoracic aorta, hypothermia was employed in all cases. The anesthetized dogs were positioned on crushed ice contained in a plastic bag on the operating table, and temperatures were followed by means of a rectal thermometer. At the time of the occlusion of the aorta the temperature ranged from 28 to 31 C. After implantation of the graft, the plastic bag containing the crushed ice was removed. Administration of oxygen through the endotracheal tube was continued until temperatures rose to 30 C.

All operations were performed with aseptic technique. The grafts were placed in the thoracic aorta with use of a long left-lateral seventh-intercostal incision. After the appropriate number of intercostal vessels had been ligated and divided, a 5 cm. segment of the thoracic aorta, carefully measured, was excised between Potts-Smith Aorta Clamps. The homografts were generally fixed to

* HT-5F nylon filter fabric. Equipment Development Company, Inc., 368 Bloomfield Ave., Montclair, N. J.

† PE-2600 Polythene film, 0.0015 in. thickness. Clay-Adams Company, Inc., 308 Washington Street, Chicago.

‡ 24 F nylon fabric. The Stehli Company, Inc., 1372 Broadway, New York.

§ Through the courtesy of Dr. C. E. Irion, Ben-Mont Papers, Inc., Bennington, Vermont.

‖ References 1 and 4. Supplied through the courtesy of Mr. T. P. Mulligan, Carbide & Carbon Chemicals Corporation, Division of Union Carbide & Carbon Corporation, 30 East 42d St., New York 17.

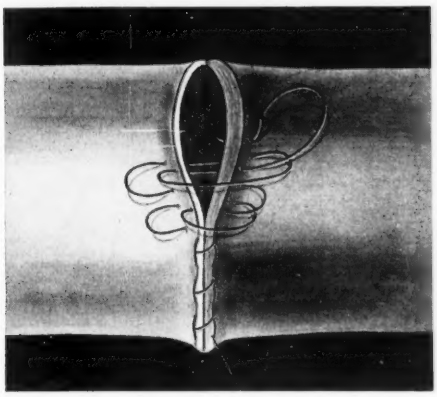


Fig. 2.—Drawing illustrating the type of suture used.

the aorta with continuous everting mattress sutures of 00000 arterial nonabsorbable (silk) sutures with swedged-on small round needles. In a few cases the anastomosis was carried out with a continuous everting mattress suture placed in such a way that after each mattress stitch the everted edge was caught with a simple locking stitch (Fig. 2). This was the type of suture used for insertion of all grafts of plastic materials. In the use of the Vinyon-N graft it was necessary to turn cuffs of ¼ in. before implanting in order to prevent fraying of the ends of the plastic material. After insertion all grafts were covered with pleura, and in a few cases in which pervious plastic grafts were used small pieces of absorbable gelatin sponge (Gelfoam) were placed about the grafts.

The grafts in all dogs killed were removed with a short segment of aorta above and below, carefully washed with saline solution, and then distended by intraluminal injection of formalin after ligation of the ends. Photographs were taken, and cross and longitudinal sections were cut and stained with hematoxylin and eosin. For comparison of the various types of grafts, all results were classified grossly according to Table 1 if the animals were killed and by determining the patency of the femoral arteries in the animals which were still alive.

OBSERVATIONS WITH FREEZE-DRIED HOMOGRAFTS

Freeze-dried homografts were inserted in 19 dogs (Table 2). Ten grafts were examined at intervals of from 3 to 166 days after implantation. All had remained patent except one (No. 620), which had thrombosed at the distal anastomosis three days after insertion. Of these 10 grafts, 9 were classified as either excellent or good, representing 90% of the freeze-dried homografts examined. The remaining nine dogs in this series are living with grafts from 110 to 150 days old. These animals all have good femoral pulses.

All operators concurred that, of the five types of grafts studied, the freeze-dried homograft was the easiest to insert and afforded the greatest security from immediate bleeding. On gross examination this type of graft had a smooth lining, a nondilated wall, and a thin but substantial envelopment of fibrous tissue. On microscopic examination the fibrinoid lining was thin. Wedges of fibrocellular tissue extended in from the edges of the host vessel, becoming sparse in the center of the graft. The innermost layer had an endothelial-like appearance at the ends of the

TABLE 1.—*Classification of Results*

1. Excellent.....	A.	Widely patent
	B.	Thin smooth lining
	C.	No external clots or constriction
2. Good.....	A.	Widely patent
	B.	Essentially smooth lining
		(a) Minimal erosion
		(b) Minimal degenerative changes
	C.	No external constriction but minimal clots
3. Satisfactory.....	A.	Functional vessel with narrowed lumen
	B.	Rough irregular lining
		(a) Mural thrombus
		(b) Excessive intraluminal fibrinous reaction
	C.	External constriction
		(a) Large clots
		(b) Excessive fibrinous reaction
4. Poor.....	A.	Failure as a conduit
		(a) Exsanguination through graft
		(b) Disruption of graft
		(c) Occluding thrombus
5. Poor Technical....	A.	Failure as a conduit traceable to a technical error

TABLE 2.—*Observations with the Use of Freeze-Dried Homografts*

Number of Animal	Period of Observation, Days	Occluding Thrombus	External Clot	Mural Thrombus	Disruption	Degenerative Change	Rough Intimal Lining	Exsanguination	Technical Error
				Killed					
620	3	+	0	0	0	0	0	0	0
706	3	0	0	0	0	0	0	0	0
720	7	0	0	0	0	0	0	0	0
723	14	0	0	0	0	0	0	0	0
735	41	0	0	0	0	0	0	0	0
601	62	0	0	0	0	0	0	0	0
615	62	0	0	+	0	0	0	0	0
997	150	0	0	0	0	0	0	0	0
605	130	0	0	0	0	0	0	0	0
956	166	0	0	0	0	0	0	0	0
				Alive					
600	150	0	0	0	0	0	0	0	0
604	146	0	0	0	0	0	0	0	0
621	142	0	0	0	0	0	0	0	0
616	139	0	0	0	0	0	0	0	0
626	132	0	0	0	0	0	0	0	0
627	132	0	0	0	0	0	0	0	0
634	125	0	0	0	0	0	0	0	0
637	123	0	0	0	0	0	0	0	0
651	110	0	0	0	0	0	0	0	0

TABLE 3.—*Observations with the Use of Grafts Made of Nylon Filter Fabric*

Number of Animal	Period of Observation, Days	Occluding Thrombus	External Clot	Mural Thrombus	Disruption	Degenerative Change	Rough Intimal Lining	Exsanguination	Technical Error
				Killed					
652	7	0	0	0	0	0	0	0	0
759	30	0	0	0	0	0	0	0	0
709	14	0	0	0	0	0	0	0	0
617	44	0	0	0	0	0	0	0	0
1000	58	0	0	+	0	0	+	0	0
986	58	+	+	0	0	0	0	0	0
936	65	0	0	0	0	0	0	0	0
684	68	0	+	0	0	0	+	0	0
882	120	0	0	0	0	0	0	0	0
985	170	0	0	0	0	+	0	0	0
925	178	0	+	+	0	0	+	0	0
934	180	0	+	++	0	0	+	0	0
				Alive					
974	180	0	0	0	0	0	0	0	0
633	125	0	0	0	0	0	0	0	0
643	118	0	0	0	0	0	0	0	0
645	115	0	0	0	0	0	0	0	0
757	49	0	0	0	0	0	0	0	0
758	44	0	0	0	0	0	0	0	0

graft, but in none of our cases had this layer completely lined the tube. No recognizable degenerative changes were found in the graft wall. The fibrous reaction around the homograft was composed of a relatively small number of layers of fibroblastic cells.

OBSERVATIONS WITH GRAFTS MADE WITH NYLON FILTER FABRIC

Aortic tubes made of nylon filter fabric were implanted in 19 dogs (Table 3). Twelve grafts were examined at intervals of from 7 to 180 days (Fig. 3). All had remained patent except one (No. 986), which had been occluded by a large thrombus and surrounded by a large external clot two months after insertion. Of these 12 grafts, 10 were classified as either excellent or good, representing 83% of the grafts of nylon filter fabric examined. The remaining seven dogs are still living, and their grafts are 44 to 180 days old. All these animals have good femoral pulses.

Although grafts of this fabric were technically more difficult to interpolate than homografts, all the operators felt that they were the easiest of the plastic grafts to insert. The fabric offered resistance to the needle point just slightly greater than that of normal tissue, cuffs were unnecessary, and the edges of the graft coapted nicely with those of the host vessel. Significant bleeding through the graft wall was not encountered. After completion of the anastomosis, the distal occluding Potts-Smith clamp was removed 30 seconds before the proximal one. A minimal amount of sweating occurred through the apertures in the fabric. On removal of the proximal clamp, the sweating was more marked for a few seconds and then ceased. By covering the graft with gauze sponges, held in place with gentle digital pressure, the usual amount of blood loss was limited to from 10 to 40 cc. On gross examination these grafts looked very good, the tubes in general being smoothly lined and widely patent, with a minimum of external fibrous reaction. Microscopic examination revealed that a fibrinoid material containing an inflamatory infiltrate rapidly formed a smooth surface within the lumen. Gradually this fibrinoid material was invaded by fibroblasts via three portals. The greatest activity occurred first at the junction of the host vessel with the graft, next at the longitudinal seam of the plastic tube, and, thirdly, through the apertures in the fabric. As in the homografts, the fibroblasts were sparser in the fibrinoid lining at the center of the graft. The innermost layer of the lining had an endothelial-like appearance. In the older grafts the cellular fibrous tissue was transformed into a more collagenous tissue. Calcification in the deeper layers of the fibrinous lining of the graft was seen in a single instance (No. 985).

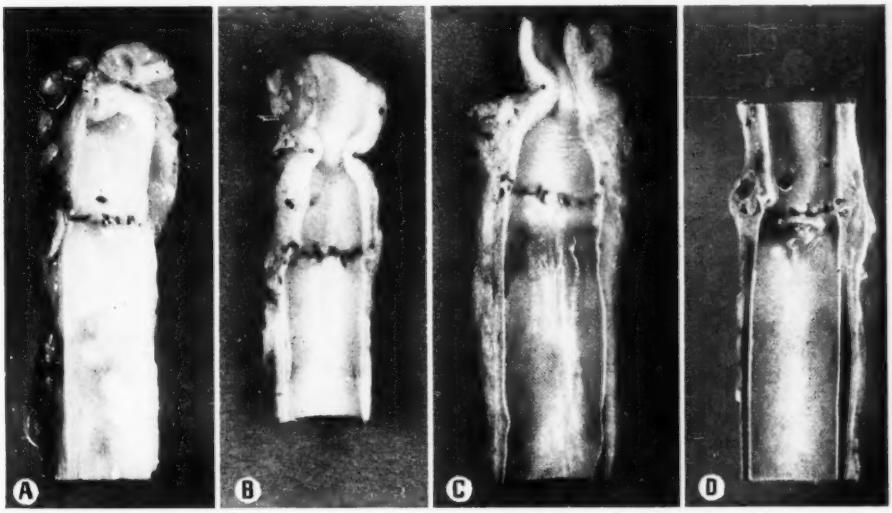


Fig. 3.—Photographs of four nylon filter fabric grafts. *A* (No. 985), 180 days; *B* (No. 882), 120 days; *C* (No. 936), 60 days, and *D* (No. 759), 30 days after implantation. The lining membrane is smooth and becomes thicker with the passage of time.

The fabric of the graft was incorporated in fibrinous tissue composed of layers of fibroblastic cells and collagenous tissue (Fig. 4).

OBSERVATIONS WITH NYLON-POLYETHYLENE-NYLON GRAFTS

Aortic tubes made of a double layer of nylon and a single layer of polyethylene were inserted in 19 dogs (Table 4). Twelve grafts were examined at intervals of from 1 to 238 days. In four of these grafts (Nos. 941, 993, 908, and 958), an occluding thrombus was noted on the 1st, 6th, 7th, and 21st days

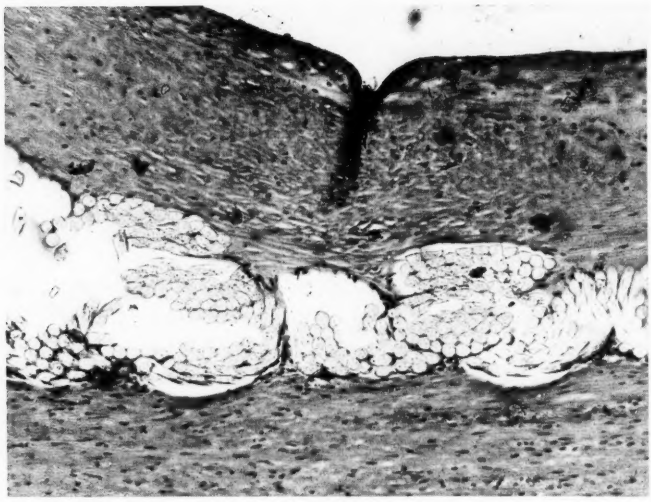


Fig. 4. — Photomicrograph of hematoxylin-and-eosin-stained section of nylon filter fabric graft 120 days old (No. 936). The smooth fibrocellular layer inside, the invasion of fibroblasts between the strands of yarn, and the incorporation of the plastic scaffold in the newly formed vessel are seen.

following insertion. The thrombotic occlusion in one of these grafts (No. 993) was attributed to a technical error. One dog (No. 988½) died of exsanguination from a technically faulty anastomosis. Seven of the grafts examined were classified as either excellent or good, representing 58% of this group. There are seven dogs in this series still living 56 to 170 days after operation. All these animals have good femoral pulses.

The operators felt that this type of material was more difficult to use than the nylon filter fabric because of its greater stiffness. Significant bleeding did not occur, except in one case (No. 988½), in which it was due to a technical error. Occasionally a small transient leak was noted in some portion of the line of anastomosis or along a seam and could be readily controlled by brief gauze packing or a single stitch. On gross examination the lining was generally more irregular than that of the homograft and mural thrombi were more frequent, but the external fibrous reaction was about the same. Microscopic studies revealed that grafts of this material differed

TABLE 4.—*Observations with the Use of Grafts Made of Two Layers of Nylon Fused to One Layer of Polyethylene*

Number of Animal	Period of Observation, Days	Occluding Thrombus	External Clot	Mural Thrombus	Disruption	Degenerative Change	Rough Intimal Lining	Exsanguination	Technical Error
				Killed					
988½	0	0	0	0	0	0	0	+	+
941	1	+	0	0	0	0	0	0	0
992	1	0	0	0	0	0	0	0	0
743	5	0	0	0	0	0	+	0	0
993	6	+	0	0	0	0	0	+	+
908	7	+	0	0	0	0	0	0	0
680	14	0	0	0	0	0	0	0	0
958	21	+	0	0	0	0	0	0	0
902	42	0	0	0	0	0	0	0	0
663	60	0	0	0	0	0	+	0	0
900	167	0	0	0	0	0	0	0	0
932	238	0	0	0	0	0	+	0	0
				Alive					
981	170	0	0	0	0	0	0	0	0
989	166	0	0	0	0	0	0	0	0
996	159	0	0	0	0	0	0	0	0
748	60	0	0	0	0	0	0	0	0
749	56	0	0	0	0	0	0	0	0

TABLE 5.—*Observations with the Use of Grafts Made of Nylon and Polyethylene*

Number of Animal	Period of Observation, Days	Occluding Thrombus	External Clot	Mural Thrombus	Disruption	Degenerative Change	Rough Intimal Lining	Exsanguination	Technical Error
				Killed					
743½	0	0	0	0	0	0	0	+	+
957	1	+	0	0	0	0	0	0	0
756	1	0	+	0	0	0	0	+	0
927	3	+	+	0	0	0	0	0	0
973	6	0	0	0	0	0	0	0	0
994	6	0	0	0	+	0	0	0	+
664	14	0	0	0	0	0	0	0	0
988	21	0	0	0	0	0	0	0	0
915	38	0	+	0	0	0	+	0	0
931	28	0	0	0	0	0	0	0	0
665	60	0	0	+	0	0	+	0	0
998	160	0	+	+	0	0	+	0	0
980	184	0	+	+	0	0	+	0	0
935	217	0	0	0	0	0	0	0	0
922	195	0	0	+	0	0	+	0	0
559	30	+	0	0	0	0	0	0	0
				Alive					
987	170	0	0	0	0	0	0	0	0
990	166	0	0	0	0	0	0	0	0
995	159	0	0	0	0	0	0	0	0
642	118	0	0	0	0	0	0	0	0
747	60	0	0	0	0	0	0	0	0
753	50	0	0	0	0	0	0	0	0

TABLE 6.—*Observations with the Use of Grafts Made of Vinyon-N Cloth*

Number of Animal	Period of Observation, Days	Occluding Thrombus	External Clot	Mural Thrombus	Disruption	Degenerative Change	Rough Intimal Lining	Exsanguination	Technical Error
				Killed					
936½	0	0	0	0	0	0	0	+	0
945	½	0	+	0	0	0	0	+	0
1001	1	+	0	+	0	0	0	0	0
671	1	+	+	+	0	0	0	0	0
710	1	+	+	+	0	0	0	0	0
733	14	0	+	0	0	0	0	0	0
681	56	0	0	+	0	0	+	0	0
946	90	0	0	0	0	0	0	0	0
954	120	0	0	+	0	0	+	0	0
628	120	0	0	0	0	0	0	0	0
944	154	0	0	0	0	0	0	0	0
938	158	+	0	+	0	0	+	0	0
968	165	0	0	0	0	0	0	0	0
955	180	0	0	0	0	0	0	0	0
				Alive					
960	187	0	0	0	0	0	0	0	0
629	130	0	0	0	0	0	0	0	0

from those of nylon filter fabric in essentially two ways. First, the fibrinoid lining of the graft tended to be thicker than that of the nylon filter fabric, and, secondly, the fibroblasts were more sparse in the center of the graft, particularly on the side opposite the longitudinal seam. Areas with a good fibrocellular lining had an endothelial-like surface. The other surfaces were covered only by organized fibrin when examined 167 and 238 days, respectively, after implantation (Nos. 900 and 932). No calcification was found in any of these specimens, although in a previous study it was noted in one instance in a graft 265 days old. The new adventitial layer outside the plastic graft tended to be composed of less dense fibrous tissue than that on the interior.

OBSERVATIONS WITH NYLON-POLYETHYLENE GRAFTS

Aortic tubes made of nylon fused with polyethylene by impulse sealing were inserted in 23 dogs (Table 5). Sixteen grafts were examined at intervals of from 1 to 217 days. Ten of the sixteen grafts remained patent, and only eight were classified as either excellent or good, representing 50% of the total. The seven remaining dogs are all living with grafts 50 to 170 days old. They all have good femoral pulses.

All operators agreed that the ease of insertion of the grafts made of the commercially fused nylon-polyethylene was greater than that of the grafts made of the hand-fused nylon-polyethylene but less than all the other types studied. Bleeding was not encountered through the wall of the tubes, but if there were any accidental needle puncture holes in the graft alarming, if not fatal, hemorrhage occurred. The gross appearance of the new aortas built up about these grafts was the poorest of all. The lining was frequently roughened with large mural thrombi or with thickened areas of fibrous lining. Large clots surrounding the graft were found frequently. Microscopic examination of these grafts revealed no appreciable difference from those grafts constructed from two layers of nylon fused with a single layer of polyethylene.

OBSERVATIONS WITH GRAFTS MADE WITH VINYON-N CLOTH

Aortic grafts made of Vinyon-N cloth were inserted in 16 dogs (Table 6). Fourteen grafts were examined at intervals of from 1 to 180 days (Fig. 5). Six were classified as either excellent or good, representing 43% of this group. Two dogs are still living with grafts 130 and 187 days old. Both animals have good femoral pulses.

The ease of satisfactorily implanting prostheses made of Vinyon-N cloth was much less than that experienced when using prostheses made of nylon filter fabric. The cuffed ends of the Vinyon-N cloth tended to wrinkle at the junction with the host vessel, particularly if there was some discrepancy in the diameters of the host vessel and graft. Marked wrinkling seemed to increase thrombosis. In our hands the greatest disadvantage of these prostheses was the troublesome bleeding that occurred through the interstices of the cloth upon release of the aortic occlusion. In an effort to seal the interstices of the cloth with fibrin before exposing the graft to the high intraluminal pressure of the descending aorta, all grafts were saturated with blood during their insertion and were then exposed for approximately 30 seconds to low pressure retrograde blood flow by removing the distal occluding aortic clamp. In vitro pre-

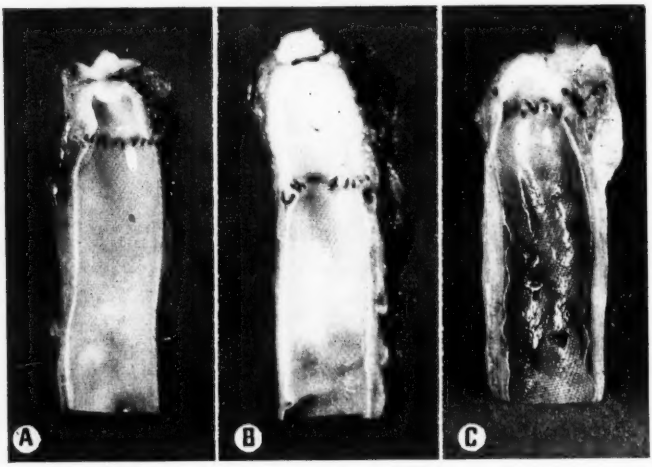


Fig. 5.—Photographs of three Vinyon-N grafts. *A* (No. 968), 180 days; *B* (No. 628), 120 days, and *C* (No. 681), 60 days after implantation. All grafts have a uniform, essentially smooth lining.

clotting [4] of the prosthesis was not employed. Brisk bleeding through the graft was generally encountered, and in some cases (Nos. 936½ and 945) this prevented recognition of blood loss through the suture line, with resultant irreversible hemorrhagic shock. To minimize bleeding and to expedite clotting about the wall of the graft, loose gauze packing with light digital pressure was employed. This seemed to be rather effective. The highest incidence of early thrombotic occlusion occurred in this series. The thrombosis was attributed to two possible causes: Either it was an aftermath of controlling some brisk bleeding by reapplying the occluding clamps to the aorta, to allow further time for the clotting mechanism to seal the interstices of the cloth, or it was due to wrinkling of the cuffed ends of the graft at the junction with the host vessel. Both of these basic difficulties, troublesome bleeding through the graft and the increased tendency toward wrinkling at the suture line, were peculiar to grafts made of Vinyon-N cloth.

On gross examination the Vinyon-N grafts were very similar to those made of nylon filter fabric (Fig. 5). The lining in the Vinyon-N grafts tended to be slightly thinner than the lining in the nylon filter fabric on microscopic examination and tended to show an earlier infiltration of cells in the fibrinoid layer throughout the entire circumference of the graft.

COMMENT

In the present study a few types of plastic arterial prostheses have been compared with freeze-dried homografts in an effort to determine whether any is a suitable substitute for the homograft from the standpoint of ease of insertion, security from hemorrhage, low risk of thrombosis, and a good gross and microscopic appearance of the graft. In order to make the results from the use of the plastic prostheses and the homografts comparable, all grafts were of a standard length and diameter and were inserted in dogs of the same size, and an equal number of grafts of each type were implanted and then examined after identical periods of observation. Five operators inserted roughly the same number of grafts of the various types. Since these studies extend only over a period of months, they must naturally be considered preliminary.

Of the various plastic materials studied to date, the nylon filter fabric makes the best arterial prosthesis, as judged from these standpoints. Altogether it is eminently satisfactory. A few of these grafts, however, were surrounded by a thrombus, and, indeed, this constituted the major single imperfection. Because these grafts did not leak blood significantly and no bleeding was noted at the time of repleuralization, this late clot formation is difficult to explain. Since the grafts are inserted under conditions of hypothermic hypotension,[6] it is conceivable that with return of normal pressure some blood may leak through the wall of the graft or the suture line or that periaortic vessels may bleed. These possibilities are now being studied. It is entirely possible that more careful observation for a short while after interpolation of these grafts will eliminate these rare difficulties. Another possible disadvantage is calcification in the fibrous inner lining. This was noted in a single animal and in one with an otherwise good result.

The next best results were obtained with the two types of grafts constructed of nylon fused with polyethylene. Although the commercially fused material was easier to work with than that fused by hand, there was a greater tendency in the former for leakage of blood from needle holes along the anastomosis and seam. The over-all results were about the same, and these results were not significantly different from those previously reported.[2] Endothelialization of these grafts was not as rapid or as complete in any given period of time as it was with the nylon filter fabric or Vinyon-N grafts. Although the security from hemorrhage with these impervious grafts constituted a definite immediate advantage, this was outweighed by the late development of a thicker and more irregular fibrous lining, with narrowing of the lumen, and this was particularly true in vessels of very small diameter. The grafts of nylon filter fabric also

permitted only minimum loss of blood through their walls but, in contrast, allowed easy ingress of fibroblasts from the surrounding host tissues into the fibrous lining of the lumen, with an apparently favorable influence in the laying down of a smooth membrane of restricted thickness.

Our poorest results were obtained with the Vinyon-N grafts, although the results with grafts of this fabric were decidedly mixed. The animals which survived had grafts that looked good grossly and microscopically. However, in our hands there was too high an incidence of poor results, and such was the case in the study of D'Angelo and his colleagues.[5] The two difficulties encountered, brisk bleeding and thrombosis, were directly traceable to the porosity of the cloth used.

Plastic grafts are a little more difficult to insert properly than homografts. In spite of the fact that the material may be impervious or nearly impervious to blood, there is more chance of moderate to severe blood loss than with the homograft, either from imperfect coaptation with the host aorta or from a leak along the seam or from a needle puncture hole. During the first six months after implantation, some of the grafts really approach perfection from the standpoint of good endothelial lining, function, and absence of clots. Yet this has not been universally true up to the present time, and minor imperfections such as erosion of the lining or small mural thrombi are noted in some. Hufnagel ¶ has emphasized the importance of washing the plastic material in order to get rid of the foreign matter that accumulates on the surface of the fiber during the processing of the cloth. None of our materials was washed, and the minor imperfections noted may have been due to these impurities. Since this study was completed, we have inserted a number of grafts of washed nylon filter fabric. Obviously something is removed by this washing, since the washed and unwashed cloth differ in feel, tendency to fraying, and perviousness to blood. Although relatively small tubes of certain plastics, such as the nylon filter fabric, can be inserted in the defects of the dog's aorta with a very low incidence of thrombosis, and, although thrombosis of plastic aortic and aortic bifurcation grafts has not been observed in our clinical experience, we are not certain that such grafts would prove successful in replacement of segments of relatively small peripheral arteries in man.

The efforts of Edwards and Tapp[9] to develop a plastic tube suitable for use in peripheral arterial replacement are interesting. They have been investigating the use of braided seamless nylon tubes which have been treated with formic acid in order to solve the problem of easy frayability, siliconed to prevent excessive loss of blood through the graft wall, and crimped in an accordian-like fashion in order to prevent wrinkling when bent. The results are very encouraging.

Although the plastic grafts as judged from immediate and relatively short-term results are not as ideal as arterial homografts, they have certain definite advantages. Chief among them are their ready availability and the ease of their acquisition and sterilization. They are very adaptable to requirements of unusual size and can be momentarily constructed to fit into an arterial defect of any given length and circumference. This was evident in a patient recently treated who had ectasia of the aorta above and below a thoracic aneurysm, necessitating a graft 16 cm. in circumference. Some disadvantages of homografts not evident in short-term studies must be kept in mind. Late degenerative changes have been noted experimentally by almost all investigators, and calcification has been observed in some clinical cases.[10] How long the elastic tissue in the media of the graft will last is uncertain,[11] and how great is the ultimate danger of aneurysmal formation is clinically unknown, though it has not proved a significant problem thus far. It seems reasonable to assume that with the passage of time there will be less likelihood of aneurysmal expansion of aortas laid down about plastic prostheses than of those incorporating homografts.

¶ References 7 and 8.

Certainly the development of the ideal pliable plastic or other fabric prosthesis seems promising and of sufficient importance to justify continuing the search.

SUMMARY

A comparison is made between certain pliable plastic tubes and freeze-dried aortic homografts. The plastics have the advantage of ready availability, ease of acquisition and sterilization, and adaptability to various requirements of size, shape, and length. Of the plastics studied, a nylon filter fabric gave the best over-all results. Though none of the plastics has proved as ideal as homografts in relatively short-term studies, it is possible that long-term results with plastic prostheses may prove superior.

REFERENCES

1. Voorhees, G. B., Jr.; Jaretzki, A., III, and Blakemore, G. H.: The Use of Tubes Constructed from Vinyon "N" Cloth in Bridging Arterial Defects, Ann. Surg. **135**:332, 1952.

2. Shumacker, H. B., Jr.; Harris, E. J., and Siderys, H.: Pliable Plastic Tubes as Aortic Substitutes, Surgery **37**:80, 1955.

3. Shumacker, H. B., Jr., and King, H.: The Use of Pliable Plastic Tubes as Aortic Substitutes in Man, Surg., Gynec. & Obst. **99**:287, 1954.

4. Blakemore, A. H., and Voorhees, A. B., Jr.: The Use of Tubes Constructed from Vinyon "N" Cloth in Bridging Arterial Defects—Experimental and Clinical, Ann. Surg. **140**:324, 1954.

5. D'Angelo, G. J.; Benson, W. R., and Grimson, K. S.: Vinyon-N Cloth Tube for Bridging Arterial Defects, A. M. A. Arch. Surg. **70**:39, 1955.

6. Deterling, R. A., Jr.; Nelson, E.; Bhonslay, S., and Howland, W.: Study of Basic Physiologic Changes Associated with Hypothermia, A. M. A. Arch. Surg. **70**:87, 1955.

7. Hufnagel, C. A., and Rabil, P.: Replacement of Arterial Segments, Utilizing Flexible Orlon Prostheses, A. M. A. Arch. Surg. **70**:105, 1955.

8. Hufnagel, C. A.: The Use of Rigid and Flexible Plastic Prostheses for Arterial Replacement, Surgery **37**:165, 1955.

9. Edwards, W. S., and Tapp, J. S.: Braided Textile Tubes as Arterial Grafts, Surgery **38**:61, 1955.

10. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953.

11. Coleman, C. C., Jr.; Deterling, R. A., Jr., and Parshley, M. S.: Some Long Term Observations on Aortic Homografts, Surgery **37**:64, 1955.

Peripheral Arteriosclerotic Vascular Disease in Diabetics

Results from Lumbar Sympathectomy and Comparative Analysis with Nondiabetic Patients

ROBERT E. L. BERRY, M.D.
and
C. THOMAS FLOTTE, M.D., Ann Arbor, Mich.

The most important degenerative lesions concomitant with diabetes mellitus are those of the vascular system. Not only do these vascular lesions give rise to clinically important diseases involving the retina of the eye, coronary arteries, kidneys, nervous system, and all elements of the peripheral vascular tree, but they remain the most common cause of death in diabetics.[1] Because of the association of diabetes and arteriosclerosis, the observation that the vascular lesions are of secondary causal relationship has been widely accepted. Moschowitz, however, has compared the incidence of hyperplastic arteriosclerosis in the aorta and pulmonary and coronary arteries of diabetics and nondiabetics dying of carcinoma, peptic ulcer, and essential hypertension. There was no significant difference.[2] Furthermore, he found that in older diabetics 36% of men and 17.5% of women had a simultaneous onset of both diabetes and arteriosclerosis or that the diabetes developed subsequent to arteriosclerotic involvement. Boas has observed that preexistent diabetes does not necessarily accelerate the development of arteriosclerosis and that the two diseases seem to develop quite independently. He also states that because more diabetic women than men are affected a constitutional predisposition must be present that is more widely distributed and potent in the female.[3]

Despite defects in our knowledge of the relationship between diabetes and arteriosclerosis, it has been well established that a definite association exists between the diabetic state and the incidence of clinically significant arteriosclerotic peripheral vascular disease. The number of diabetics in the United States is not known. It has been estimated that there are about 1,500,000 known diabetics and a similar number who have the disease but are unaware of it.[4] In the general population, therefore, the ratio of nondiabetics to diabetics is about 55 : 1. The incidence is much higher in those persons developing clinical peripheral arterial insufficiency. Of 275 patients with arteriosclerosis obliterans undergoing lumbar sympathectomy during the years 1945-1952 at the University of Michigan Hospital, 93 (33.9%) had clinically proved diabetes. The results following operation in these patients and comparison with those observed in 182 nondiabetic patients are the subject of this report.

AGE AND SEX INCIDENCE OF DIABETES

Age distribution is shown in Figure 1. The greatest number of diabetics were 55 to 65 years of age, but the highest incidence occurred in the 65 to 75 age group (44.1%). It was of interest to observe that only 15% of patients under 45 had diabetes. A consolidation of age groups is shown in Table 1. Twenty-three diabetics (25%) were under 55 years of age; 37 (40%) were between

Received for publication April 25, 1955.

From the Department of Surgery, University of Michigan, Ann Arbor, Michigan.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

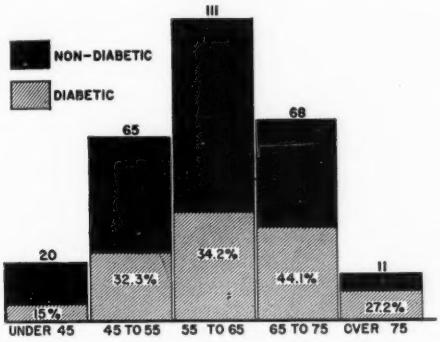


Fig. 1.—Age distribution and incidence of diabetes of 275 patients undergoing lumbar sympathectomy for arteriosclerotic vascular disease.

55 and 65, and 33 (35%) were more than 65. Age groups of nondiabetics were as follows: under 55 years, 62 (34%); from 55 to 65 years, 74 (41%), and over 65 years, 46 (25%). The incidence of symptomatic peripheral vascular ischemia was higher

TABLE 1.—*Age Distribution of Patients Undergoing Lumbar Sympathectomy*

	Diabetic	Nondiabetic
Below 55	23 (25%)	62 (34%)
Between 55 and 65	37 (40%)	74 (41%)
Above 65	33 (35%)	46 (25%)

in nondiabetics under 55 than in diabetics of the same age group. There was, however, a comparably higher incidence of diabetic patients after the age of 65.

Sex distribution is presented in Figure 2. Males outnumbered females 4 to 1. Of 220 male patients, 50 (22%) had proved diabetes. The incidence of diabetes in females was much higher. Of 55 women, 43 (79%) were diabetic. The reasons for the higher incidence of arteriosclerotic disease in men is not known. It has been pointed out that young men have a higher concentration of the plasma β-lipoproteins, a larger content of S_f 10-20 lipoproteins, and a lower concentration of α-lipoproteins than women. Women, furthermore, have a larger number of mast cells, a presumed source of heparin that aids in clearing alimentary hyperlipemia. Consideration has also been given the observation that testosterone administered parenterally raises the level of β-lipoproteins and estrogens lower it.[5] The significance of these findings awaits further investigation.

RESULTS

Diabetics Without Tissue Necrosis.—Only 17 (18%) diabetic patients were without ulceration or gangrene at the time of hospitalization for peripheral vascular disease. Of these, three had intermittent claudication of moderate severity as the only symptom, six had moderate rest pain with attendant intermittent claudication, and eight had severe rest pain. Only four of the latter had concomitant claudication.

Results following sympathectomy and a comparison with the 93 nondiabetics without tissue necrosis are shown in Table 2. Good

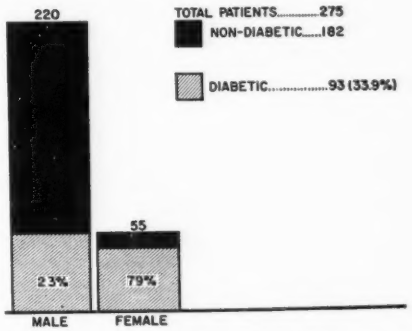


Fig. 2.—Sex distribution and incidence of diabetes in sympathectomized patients.

results were obtained in six (35%) and a poor result without subsequent amputation in five (30%) of these patients. In 17 diabetics 5 sympathectomized legs were amputated, an amputation rate of 30%, and 8 patients (47%) are now dead, the average

TABLE 2.—*Results Following Lumbar Sympathectomy in Diabetics and Nondiabetics Without Ulceration or Gangrene*

Results	Diabetics (17)	Nondiabetics (93)
Good	6 (35%)	41 (44%)
Poor; no amputation	5 (30%)	29 (31%)
Amputation	5 (30%)	17 (18%)
Dead	8 (47%)	31 (33%)

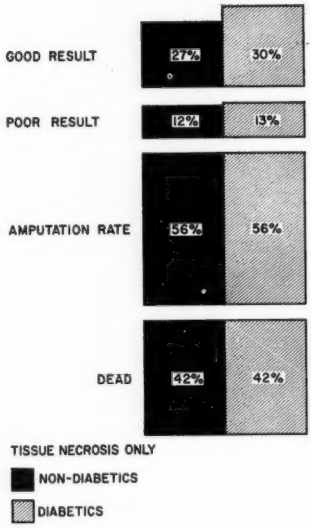


Fig. 3.—Results following lumbar sympathectomy in diabetics and nondiabetics who have developed ulceration or gangrene.

survival time after leaving the hospital being less than 15 months.

Good results were obtained in 41 (44%) nondiabetic patients without tissue necrosis and poor results without amputation in 29 (31%). Seventeen patients underwent amputation, an amputation rate of 18%. Thirty-one nondiabetic patients (33%) are dead, the average survival time being 25 months.

Diabetics with Tissue Necrosis.—The majority of diabetic patients in this study had had some degree of tissue necrosis upon admission to the hospital. Seventy-six (82%) were so afflicted, as compared with an incidence of 55% among nondiabetics. These figures do not include a large number of patients with extensive ulceration or gangrene who underwent amputation without prior sympathectomy because it was obvious that no benefit could be obtained.

TABLE 3.—*Results Following Lumbar Sympathectomy After Development of Ulceration and Gangrene**

Results	Diabetic (76)	Nondiabetic (93)
Good	23 (30%)	24 (27%)
Poor; no amputation	10 (13%)	11 (12%)
Amputation	43 (56%)	54 (56%)
Dead	32 (42%)	37 (42%)

* Note that percentagewise the results are essentially the same.

The results from lumbar sympathectomy in diabetics who have developed tissue necrosis and a comparison with similar nondiabetics are presented in Figure 3 and Table 3. Good results were obtained in 23 (30%), and 10 (13%) obtained no benefit but did not require subsequent amputation. Forty-three (56%) of sympathectomized limbs were amputated. Thirty-two (42%) patients are now dead, having survived an average of 26 months following operation.

When compared with nondiabetic patients with necrosis, the results observed are almost identical, as 27% obtained good results and 12% poor results without amputations; 56% of sympathectomized extremities were subsequently amputated, and 42% of the patients are dead, having again an average postoperative survival time of about 26 months. These figures would suggest that after development of tissue necrosis the presence of diabetes has little relationship to result.

A summary comparison of all diabetics and nondiabetics is presented in Figure 4 and

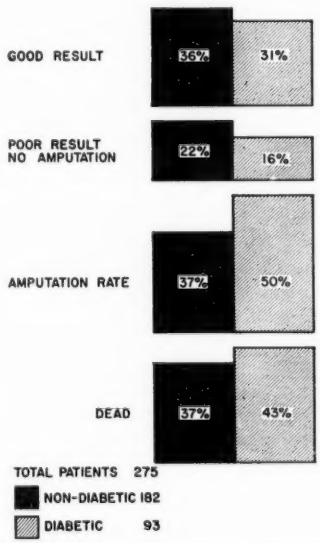


Fig. 4.—Results following lumbar sympathectomy in all diabetic and nondiabetic patients.

TABLE 4.—*Comparative Results in all Diabetics and Nondiabetics Following Lumbar Sympathectomy*

Results	Diabetic (93)	Nondiabetic (182)
Good	29 (31%)	65 (36%)
Poor; no amputation	15 (16%)	40 (22%)
Amputation	48 (50%)	71 (37%)
Dead	40 (43%)	68 (37%)

Table 4. The percentage of good results is slightly higher in nondiabetics. One half of the legs of diabetic patients eventually were amputated, as compared with 37% of nondiabetic. Forty-three per cent of diabetics are dead, as are 37% of nondiabetics, the two groups having approximately the same survival period, of about 25 months.

RELATIONSHIP OF AGE AND THE RESULT FROM LUMBAR SYMPATHECTOMY

There is an inverse relationship between age and the good results obtained from lumbar sympathectomy (Table 5). Under 55 years of age, 48% of diabetics obtained a good result, as did 44% of nondiabetics. Between 55 and 65 years, 38% of diabetics and 34% of nondiabetics achieved good results. Above 65 there was a sharp disparity in results, as 28% of nondiabetics were benefited but only 12% of diabetics obtained a good result. The results in diabetics over 65 years were so poor that this group constitutes a contraindication to operation, particularly if there is significant elevation of blood pressure, over 160 mm. Hg systolic, or evidence of cardiac or cerebral arteriosclerotic disease.

TABLE 5.—*Number and Percentage of Good Results Following Lumbar Sympathectomy Based Upon Age**

Age	Diabetics (93)	Nondiabetics (182)
Below 55	11 (48%)	27 (44%)
Between 55 and 65	14 (38%)	25 (34%)
Above 65	4 (12%)	13 (28%)

* Note that poorest results were observed in elderly diabetics.

THE EFFECT OF SEVERITY AND DURATION OF THE DIABETIC STATE AND ADEQUACY OF TREATMENT ON THE RESULT FOLLOWING SYMPATHECTOMY

It is a well-documented observation that the vascular complications of diabetes may occur despite apparent adequate insulin and dietary control of the hyperglycemia.* Inadequate control does not necessarily imply mandatory development of vascular disease. Bell,[8] after a study of 1599 autopsies on diabetic subjects, stated that the absence of vascular disease in long-term survivors could not be attributed to better control of the diabetes. This author also observed that when the onset of the disease is before 40 years of age duration has a striking influence upon the development of vascular lesions. Very few young diabetics had severe vascular disease within the first 10 years of the diabetes. Thereafter atherosclerosis became prominent in various organs. In those who died between 40 and 60 years of age, the duration of the disease is not such a prominent factor, while in those dying after the age of 60 the duration exerts but a small influence.

Diabetes of long duration does not necessarily terminate in vascular death. In older diabetics there appears to be no relation between the severity of the diabetes and the tendency toward vascular disease, as serious vascular lesions develop as frequently in those with mild as in those with severe diabetes.[8]

Severity.—For the purpose of comparison, diabetes in this study was considered mild if controlled by diet or by the administration of less than 15 units of insulin a day, of moderate severity if the daily administration of 15 to 40 units was required, and severe if more than 40 units was required daily. The largest number of patients (62) were considered as having mild diabetes, 26 moderately severe, and 5 severe. The degree of severity had little apparent influence upon the percentage of good results, amputation rate, or subsequent longevity (Fig. 5).

* References 4, 6, and 7.

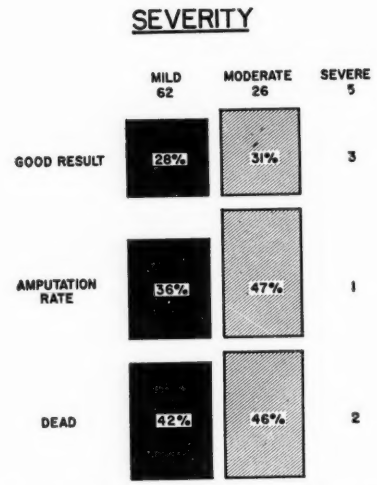


Fig. 5.—Relationship of severity of diabetes to the results from lumbar sympathectomy in 93 diabetic patients.

Duration.—Fifty-four patients who had had their disease for more than five years were considered long-term. Twenty-three having diabetes less than 5 years were classed as short-term, and 15 patients had their diabetes discovered for the first time when hospitalized for peripheral vascular complications. Duration little affected the good results from operation. Including those discovered in the hospital, short-term diabetics had a higher amputation rate. The longevity differences are not statistically significant (Fig. 6).

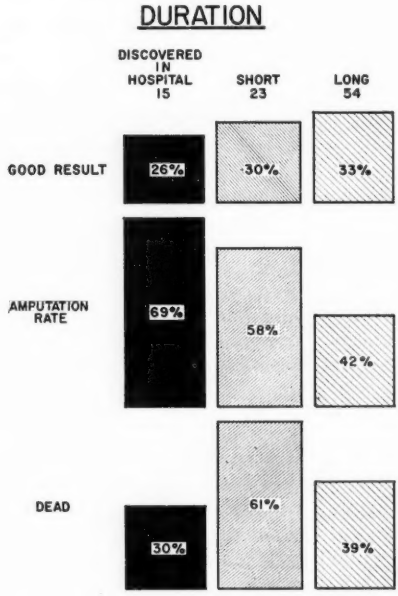


Fig. 6.—Relationship of duration of diabetes to the results from lumbar sympathectomy.

Adequacy of Treatment.—On the basis of history evaluation of the diabetic status at the time of admission 65 patients were considered to have been adequately treated, and 28, including the 15 patients whose diabetes was discovered in the hospital, were found to have been inadequately treated. The percentage of good results from operation was about the same, but the amputation rate of inadequately treated patients was higher. Longevity was essentially the same (Fig. 7).

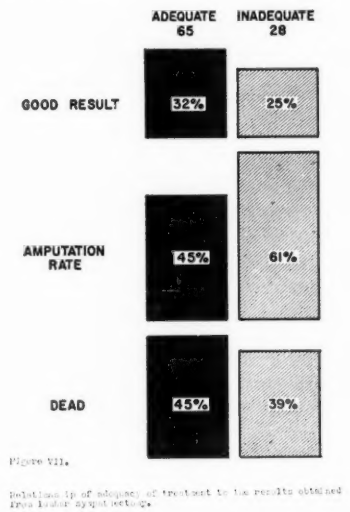


Fig. 7.—Relationship of adequacy of treatment to the results obtained from lumbar sympathectomy.

COMMENT

Nature of the Vascular Lesions.—Calcification of the media and atherosclerosis are the predominant arteriosclerotic changes in

the larger peripheral vessels of diabetics developing arterial insufficiency. The nature of the atherosclerotic lesion is the most important determinant as regards survival of the limb in both diabetics and nondiabetics. Diabetic atherosclerosis is characterized by focal thickenings of the intima in which stainable lipids can be demonstrated between and in cellular structures. The amount of lipid may vary tremendously. It is thought that the lipids enter through the blood stream, although sometimes the quantities are so great that it would appear that deposition was the result of local metabolic aberrations.[9]

Although sclerosis of the larger arteries of the lower extremities is of paramount importance in the development of peripheral ischemia, increasing emphasis has been placed upon the characteristic lesions which now seem specific for diabetes in arterioles, venules, and capillaries.[9] The hyaline change in the arteriolar wall with resultant arteriolosclerosis is characteristic of younger diabetics with disease of long duration.[8] Increased capillary fragility can be an early manifestation of impending vascular degeneration. Particularly does the association of retinal hemorrhages in young diabetics with capillary aneurysms in the retina emphasize the role of capillaries in vascular complications.[10] It is the belief of Goodman and his coworkers [11] that there is something distinct about the arteriosclerotic process in younger diabetics, as capillary disease and an earlier onset of a severer form of medial calcification produces an entirely different disease from that observed having its onset in older diabetics. The venous lesions observed in diabetic retinitis complete the involvement of all elements of the vascular tree.[12]

The Importance of Blood Lipid Concentrations.—Deposition of lipids apparently is accentuated by the presence of hypercholesteremia.[13] An increase of blood cholesterol is lacking in many diabetic patients who have marked lipid deposition, however. It would seem, therefore, that instability of cholesterol rather than increased concentration is more essential to lipid accumulation. This stability has been related to other substances, of which the phospholipids may be important as stabilizing agents. Other factors that must be considered, in addition to the concentration of cholesterol and related lipids, are the number and size of plasma chylomicrons; tissue factors, such as chondrotin sulfuric acid and other carbohydrate sulfate esters in the intima; blood pressure, and the sex hormones.† Gofman and coworkers described giant lipoprotein molecules in the sera of arteriosclerotic patients.[14] It was their opinion that coronary sclerosis was related to a particular group of lipoproteins which contain cholesterol. This work was not confirmed by Collens and Banowitch.[15]

In this series the results from sympathectomy were essentially the same in both diabetic and nondiabetic groups after the onset of gangrene or ulceration. The amputation rate, anticipated postoperative longevity, and good results were almost identical (Table 3). If ulceration or gangrene has not developed prior to sympathectomy, the results in diabetics are not so good as in nondiabetics (Table 2). The number of diabetics in this latter group is small, however, and standard error deviation prevents a reliable conclusion.

Up to age 65 the diabetic has an equal, if not slightly better, chance for a good result from sympathectomy. After 65 only 12% of diabetics obtained a good result, as compared with 28% of nondiabetics.

The incidence of gangrene in diabetic patients with symptomatic peripheral arterial disease is twice that in nondiabetics. This difference could be conceivably related to small vessel involvement with associated lessened tolerance to trauma and infection. Handelsman has observed small vessel dysfunction in a large percentage of diabetics in the presence of apparent normal peripheral circulation.[6]

Despite the diabetic's greater tendency toward gangrene, it would seem, from the data in this series, that diabetes possesses

† References 5 and 13.

singular little influence upon over-all results when compared with results in nondiabetics undergoing sympathectomy, except in patients above 65 years of age. Severity, duration, and adequacy of treatment of diabetes little affect the percentage of good results obtained or the longevity following operation. Short-term diabetics (having had the disease less than five years) and those inadequately treated have a somewhat higher amputation rate.

SUMMARY

The results from lumbar sympathectomy in 93 diabetic patients with symptomatic peripheral vascular disease have been presented and compared with results in 182 nondiabetic patients.

In the absence of ulceration or gangrene results in nondiabetics are somewhat better than in diabetic patients. After necrosis has developed, the results are essentially the same.

Below 55 years of age 48% of diabetics obtained a good result. Above 65 only 12% were benefited. The results in diabetics over 65 years of age with significant elevation of blood pressure or central nervous system or cardiac involvement are so poor that they represent a contraindication to sympathectomy.

Severity, duration, or adequacy of treatment of diabetes little affects the percentage of good results obtained. The amputation rate is higher in inadequately treated and in short-term diabetics.

The nature of the vascular lesions, blood lipid changes, and the relationship to the higher observed incidence of gangrene in diabetics have been discussed.

DISCUSSION

DR. LOUIS T. PALUMBO, Des Moines: I should like to compliment Dr. Berry and Dr. Flotte on their excellent paper and for their very careful evaluation of the results in this group of patients. Briefly I should like to relate our experiences in this field.

[Slide] During a period of four years, from 1946 to 1950, we performed 220 lumbar sympathectomies on 159 adult male patients. In this group 72 procedures were done on 49 patients with peripheral arteriosclerosis, 20 of whom were diabetic.

We found that the average age in each group was 59 years and that the patients with diabetes seemed to seek medical attention sooner than those who had just peripheral arteriosclerosis without diabetes; in fact, in this group the symptomatology existed for only one year in the diabetics.

[Slide] Our results very much parallel those of Dr. Berry as reported today. We find that these patients with diabetes have a higher incidence of gangrene, as noted on this slide, and because of this fact there are more major amputations performed. However, we have noted over a period of years that the amputation can be performed below the knee in a high percentage of cases. In this particular group we found that 60% of the patients coming to major amputation with diabetes had amputation performed below the knee, whereas in the group with peripheral arteriosclerosis alone the amputation was performed below the knee in 50% of the cases.

The complication rate during the period of hospitalization and following surgery seemed to be a little less in those patients who had diabetes. The possibility exists that we are giving the patients in this group more personal attention and in this way averting many of the complications.

[Slide] The evaluation of the results here are parallel in both groups. As Dr. Berry pointed out, the younger patient will have a better result than the older patient, and the failures in our group were in patients who were about 68 years old. That was true in both the diabetic and the nondiabetic group.

Since 1939 we have performed over 600 lumbar sympathectomies for peripheral vascular diseases, and it has been our impression, in a study of the results in these patients, that the operation has definite merit in the treatment and management of many diseases of the extremity and that it carries a very low morbidity and mortality rate.

As a result of the improvement in the circulation, we can expect in a fairly high percentage of patients improvement of their symptoms and in many cases complete relief of their symptoms.

In some persons we might delay the need for major amputation, and when an amputation is necessary I believe that we can develop a more conservative attitude and, therefore, can perform many more amputations below the knee than we formerly did.

REFERENCES

1. Bell, E. T.: Incidence of Gangrene of the Extremities in Nondiabetic and Diabetic Persons, Arch. Path. **49**:469, 1950.

2. Moschowitz, E.: The Relations of Hyperplastic Arteriosclerosis to Diabetes Mellitus, Ann. Int. Med. **34**:1137, 1951.

3. Boas, E. P.: Arteriosclerosis and Diabetes, J. Mt. Sinai Hosp. **19**:411, 1952.

4. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1952.

5. Barr, D. P.: Influence of Sex and Sex Hormones upon the Development of Atherosclerosis and upon the Lipoproteins of Plasma, J. Chron. Dis. **1**:63, 1955.

6. Root, H. F.; Marble, A., and Wilson, J. L.: Relation of Control of Diabetes to Vascular Degenerative Lesions in Young Diabetics, Tr. Am. Clin. & Climatol. A. **62**:23, 1950.

7. Dolger, N.: The Clinical Evaluation of Vascular Damage in Diabetes Mellitus, Bull. New York Acad. Med. **22**:482, 1946.

8. Bell, E. T.: A Postmortem Study of Vascular Disease in Diabetics, A. M. A. Arch. Path. **53**:444, 1952.

9. Root, H. F.: Degenerative Complications of Diabetes: A Review, J. Clin. Endocrinol. **12**:458, 1952.

10. Rodriguez, R., and Root, H. F.: Capillary Fragility and Diabetic Retinitis, with Note on Use of Rutin, New England J. Med. **238**:391, 1948.

11. Goodman, J. I., and Wasserman, J.: A Study of Atherosclerosis in a Group of Diabetic Patients, Am. J. M. Sc. **220**:30, 1950.

12. Warren, S., and LeCompte, P.: The Pathology of Diabetes Mellitus, Ed. 3, Philadelphia, Lea & Febiger, 1952.

13. Duncan, G. G.: Diabetes Mellitus, Philadelphia, W. B. Saunders Company, 1951.

14. Gofman, J. W., and Others: The Role of Lipids and Lipoproteins in Atherosclerosis, Science **111**:166, 1950.

15. Collens, W. S., and Banowitch, W. S.: Lipoprotein Studies in Diabetics with Artereosclerotic Disease, J. A. M. A. **155**:814, 1954.

16. Handelsman, M. D.; Levitt, L. M., and Conrad, H., Jr.: Small Vessel Dysfunction in Patients with Diabetes Mellitus, Am. J. M. Sc. **224**:34, 1952.

Spring Valve for Mitral Insufficiency

Preliminary Report

PRESCOTT JORDAN JR., M.D.
and
JAMES WIBLE, M.D., Detroit

The surgical attack upon acquired heart disease has progressed at a rapid pace since the advent of mitral commissurotomy in 1949.[1] The outstanding valvular defect, which still is unsolved from a surgical standpoint, is mitral insufficiency. Bailey[2] found at operation that 21.7% of patients operated upon for mitral stenosis had a significant amount of mitral insufficiency. In addition, in 5.5% of these patients the insufficiency was the major lesion.

The surgical attack on this lesion has been varied. The sling procedure, which was the first clinical approach, has now been discarded.[3] Prosthetic alleviation of the insufficiency by the use of a plastic baffle, as advocated by Harken,[4] is probably the most accepted clinical method today, along with the suturing of the valve as has been advocated by Bailey and co-workers.[5] Experimentally the mitral valve has been replaced by a polymerized methyl methacrylate (Lucite) prosthesis by Denton[6] and by a homograft of the aortic valve.* On theoretical grounds, the shortening of the dilated mitral annulus has been advocated by Davila, Mattson, O'Neill, and Glover.[7] Experimentally this has been reported by Hurwitt, Hoffert, and Ferreira.[8] Replacement of the posterior leaflet of the mitral valve with a vein graft has been reported by Gordon Murray.[9] Carter[10] has reported investing plastic balls with pericardium and placing them in the left ventricular cavity as a moving prosthesis. Johns and Blalock[11] devised a method of attaching a polyvinyl sponge to the papillary muscle to form a moving prosthesis for mitral insufficiency.

It is clear, therefore, that the final answer to this difficult problem is not at hand. We wish to present another method which is promising in the experimental laboratory and may be in itself, or with modifications, a method for alleviating some of the insufficiencies found at operation upon the mitral valve.

THEORETICAL CONSIDERATIONS

There are roughly two types of mitral insufficiencies in the human mitral valve. The first is an insufficiency with a freely moving anterior leaflet, and the second is an insufficiency in which both leaflets are thickened, fixed, and at times calcified.

In the first form, with the freely movable anterior leaflet, it is at least theoretically possible that either the shortening of the dilated annulus, as proposed by Glover and O'Neill, or the substitution of the posterior leaflet by a baffle to allow the anterior leaflet to close securely may be the solution to the problem.

In the second type, the ideal prosthesis seems to us to be one which would fulfill the following criteria:

1. It must stop mitral insufficiency.
2. It must be easily inserted into an intact circulation.
3. Ideally it should move and continue its motion for a prolonged period.
4. It should be, if not originally of living material, at least eventually covered by living tissue.

Submitted for publication April 25, 1955.

Read at the 12th Annual Meeting of the Central Surgical Association, Chicago, Feb. 18, 1955.

From the Experimental Laboratories of the Department of Surgery, Wayne University College of Medicine, and the Detroit Receiving Hospital.

Aided by a grant from the Michigan Heart Fund and the Research Fund of the Veterans Administration Hospital, Dearborn, Mich.

* Unpublished data.

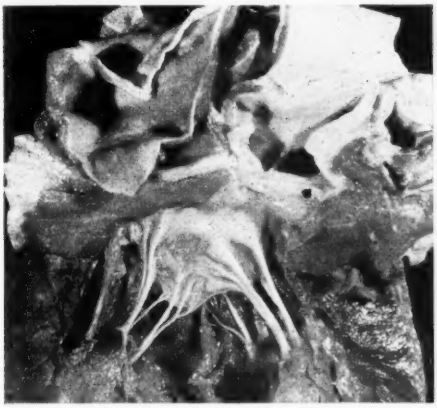


Fig. 1.—Free area between chordae tendineae under mitral valve.

5. It should not defibrinate or in any way disturb the normal elements of the blood.

6. It should not embolize or cause clot formation.

7. It should be tolerated within the chambers of the heart.

8. It should not in any cardiac cycle obstruct the normal direction of the flow of blood.

One anatomical consideration is the space between the "off-takes" of the chordae tendineae at the free edge of the leaflets. This space (Fig. 1) allows room for a moving prosthesis to be placed across the mouth of the mitral funnel without interference from intraventricular structures. In the second type of mitral insufficiency, the anterior leaflet gives a firm base against which a prosthesis may seat and not invert into the left atrium on ventricular systole. It is thus anatomically evident that a prosthesis placed in this area could obstruct the outflow tract of the aorta. Therefore, the ideal prosthesis should be one in which there is sufficient flexibility to keep it from obstructing the intraventricular portion of the aortic outflow. Further, it should have enough internal elasticity so that it will not be caught against any structure and become adherent.

The final consideration is based on our belief that it is easier to feel an insufficiency than see one. If this is valid, a method of valvular replacement must be one that does not interrupt the blood flow. Thus the replacement method must be one which allows placement within an intact circulation.

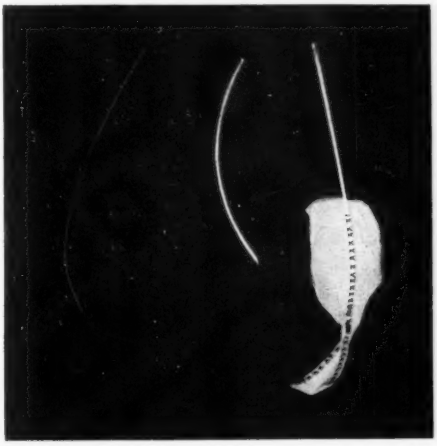
A SPRING VALVE PROSTHESIS

The experimental prosthesis which we have been investigating is composed of a metallic frame over which a double layer of nylon has been sewn (Fig. 2).

The metal chosen, Elgiloy, is a supersaturated mixture of metals, patented by the Elgin Watch Company. This alloy has several interesting properties. First, it is noncorrosive; second, it has little tissue reaction; third, it has a high modulus of elasticity and a high index of hardness, and fourth, the theoretical longevity of an Elgiloy spring moving as required in these experiments is greater than 300 years.

The method of construction is simple. It is a double band of metal with the two limbs at approximately 45 degrees from each other. The stem is spot welded at centimeter intervals so that it may be trimmed at the table. Because of the spring of the frame, the valve limbs can be folded and placed within a trocar. When the trocar is removed the valve limbs spring open within the left ventricular chamber and assume a valvular character.

Fig. 2.—Reading from left to right, Elgiloy frame, trocar, and frame covered with nylon.



METHOD

A series of 43 dogs was used in this experimental investigation. These dogs were mongrels, weighing approximately 20 to 27 kg. The problem was divided into three phases. The first phase consisted of developing a technique by which this prosthesis could be safely and easily inserted into the left ventricle. In this same phase, a method of making mitral insufficiency which was comparable with that found in humans and at the same time was compatible with some degree of longevity was evolved. The second phase consisted of making such an insufficiency and correcting it at the same operative procedure. The third phase, which has not been completed, includes making animals insufficient and allowing them to retain this insufficiency for a period of time and then correcting it by means of the spring valve.

These animals were operated upon through the left chest with surgically clean technique with use of a mechanical respirator. No digitalis or blood transfusions were used. After a number of dogs had been lost owing to pneumonia, the animals were given 200,000 units of penicillin intramuscularly daily for three to five days postoperatively. The prosthesis itself was modified several times because of difficulties encountered with its insertion. In the first group of dogs, after standardizaton of the technique, three dogs were set aside for longevity studies. Fluoroscopic examinations at two- to four-month intervals to ascertain the mobility of the valve were carried out.

During the development of a method of constructing an insufficiency, a number of spontaneous insufficiencies were found and treated by the spring valve. These preparations were included in the second group of dogs.

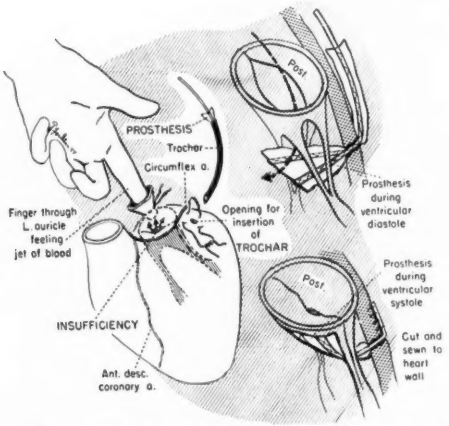


Fig. 3.—Technique of insertion and motion of prosthesis. (N. B., for purposes of illustration, the site of the insertion is not shown accurately.)

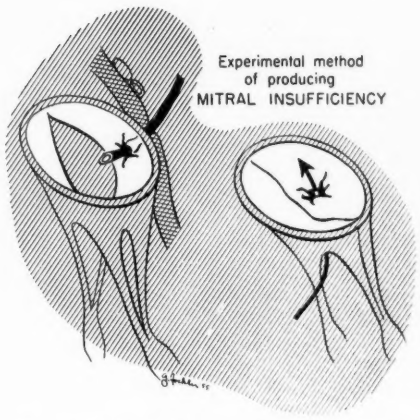


Fig. 4.—Method of producing mitral insufficiency.

In the second group of dogs, atrial pressures were taken after development of a method of making a mitral insufficiency. These were taken before an insufficiency was made and during and after placement of the spring valve.

Dogs dying or killed one week to five and one-half months after operation were autopsied, and the character of the valve and cause of death were tabulated. Histological examination of tissues and valves was made. In all dogs that survived one month to five and one-half months, blood was drawn for determination of Lee-White coagulation times.

RESULTS

The technique we now use to insert the prosthesis is illustrated in Figure 3. The left auricular appendage is entered in the usual manner, and the exploring finger locates the

TABLE 1.

		Animals, No.
Total		43
Living	10	
Died	33	
Causes of death		
1. Mitral insufficiency attempts without insertion of prosthesis (most in acute failure)		19
2. Malposition (early)		2
3. Pneumonia (one at 5½ mo.)		3
4. Heart failure		3
5. Erosion of pulmonary artery		1
6. Intestinal obstruction		1
7. Tension pneumothorax		1
8. Vomiting and aspirating		1
9. Acute blood loss		1
10. Postoperative bleeding (1 with embolization of nylon)		2
11. Unknown		1

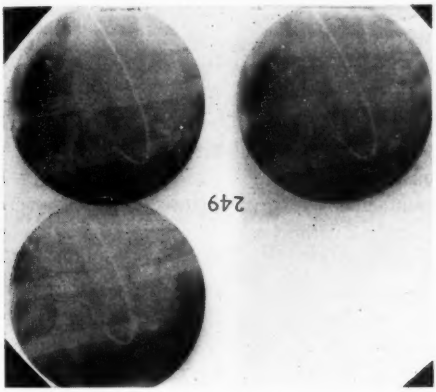
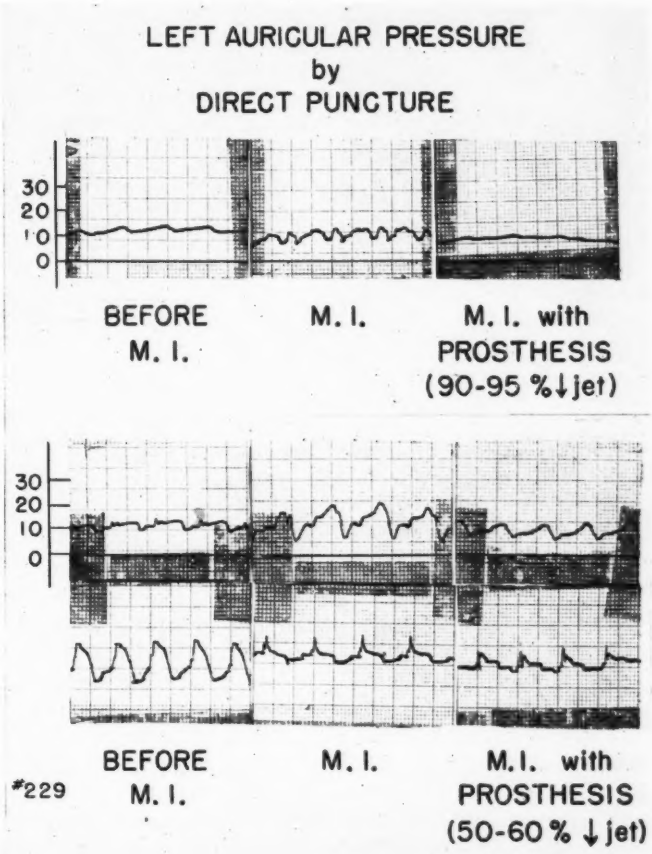


Fig. 5.—X-ray of moving valve.

TABLE 2.

	Survival to Present
Living animals	
3 with spontaneous jet and valve	5 mo.
2 with trocar punch mitral insufficiency and valve	3 mo.
3 without mitral insufficiency, valve alone	5½ mo.
2 with trocar punch mitral insufficiency to become chronic	2 wk.
	Percentage of Stoppage
Effect of prosthesis upon jet as palpated by bare fingers	
All spontaneous jets	90-100
Jets induced by trocar punch	95-100
Jets induced by other methods	20-60

Fig. 6.—Tracings of left atrial pressures.



site of the insufficiency. The midportion of the posterior leaflet is identified, and a purse-string suture is placed high on the ventricle wall just posterior to this area. The loaded trocar is introduced through the ventricular wall at right angles to the commissures and below the anterior leaflet. The trocar is withdrawn from around the valve, and the position of the prosthesis is adjusted to stop the jet of insufficiency. The valve frame is

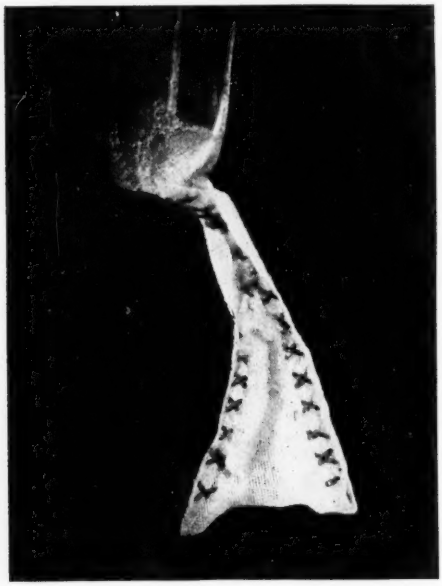


Fig. 7.—14 days after operation; endothelium extends almost to free edge of prosthesis.

trimmed and its Nylon covering sutured to the epicardium.

After we had attempted to induce insufficiency by many methods, the method which in our hands produced the best result was punching a hole in the posterior leaflet with a trocar (Fig. 4). As can be noted in Table 1, more than one-half of our mortality came from trying different methods of insufficiency production. The remaining deaths were due to either technical complications, before our method of introduction was standardized (Table 1, Items 2, 5, 9, and 10), or unavoidable complications.

Fluoroscopic examination of the surviving animals revealed that the prosthesis moved in a manner which appeared to be functional (Fig. 5). In the animals in which spontaneous jets were found and in animals that had insufficiency produced with the trocar punch (Table 2), the jet of insufficiency was concontrolled 90% to 100%, as estimated by palpation with the bare finger. Atrial pressures recorded at the operating table were compatible with the tactile estimation of the control of the jet (Fig. 6).

Autopsied animals showed that in 12 to 14 days the leaflet becomes covered with a smooth, glistening surface (Fig. 7). Fusion at the junction of the prosthesis and the left ventricle was smooth, without leaks, and quite tenacious. Microscopic examination of the nylon of the leaflet showed it to be covered with endothelial-like cells. At five and one-half months, the Elgiloy remains bright and shiny.

Lee-White coagulation time on living animals was normal, i. e., between four and nine minutes.

COMMENT

These experimental results, as outlined, are not brilliant in over-all dimensions. However, there are a number of facts which are encouraging and possibly may lead to a more adequate solution of the problem of mitral insufficiency.

This prosthesis is easily inserted into the left ventricle of the dog by the method developed. The placement of this prosthesis is by finger control, and it thus can be accurately placed into an intact circulation. Furthermore, under fluoroscopy, this prosthesis appears to move for protracted periods, and in the animals which have died or been killed the prosthesis was covered by living tissue and firmly fixed to the wall of the ventricle. The studies of the clotting mechanism demonstrate that this moving prosthesis causes no aberration in the normal clotting mechanism in dogs. Both on palpation and on recording

from the left atrium, an insufficiency, if present, is controlled acutely by the use of this prosthesis. Finally, it would appear that this moving valve is well tolerated up to five and one-half months in dogs.

It is technically conceivable that a spring valve of similar nature placed at the aortic annulus may present a more efficient approach to the problem of aortic insufficiency than present methods available.

SUMMARY

Mitral insufficiency has been arbitrarily classified into the following two groups: (*a*) that with a freely moving anterior leaflet and (*b*) that with a rigid leaflet.

The criteria of an ideal mitral prosthesis are presented.

An experimental method is presented, with use of a nylon-covered framework of metal, which can be placed simply into the left ventricle under finger control through a small trocar.

The results of this method in 43 dogs are presented; the surviving 7 dogs have been studied in regard to the ability of the spring valve to satisfy the criteria of an ideal mitral prosthesis.

A method of experimentally producing mitral insufficiency in dogs is also presented.

Mr. Thomas R. Green, of the Elgin National Watch Company, gave technical advice and supplied materials for this project.

DISCUSSION

DR. CHARLES G. JOHNSTON, Detroit: I want to take this opportunity to express my appreciation for being able to follow these studies. I have followed Dr. Wible's and Dr. Jordan's studies in the laboratory and have seen the attempts at introduction of other types of valves.

This meets one criterion that I think we must always look forward to, and that is simplicity of placement. This can be done without an open heart, with the blood flowing, so there is no need for looking at the replacement that one is putting in. It is very simple. It is introduced through the trocar, and it is placed so that one feels that the valve is seating in good position.

The question that always arises is that of whether the spring will continue to do a good job. It has been estimated that one of these prostheses will last for 300 years. I think that will probably last most of the patients' lives. This has a very high degree of elasticity, and I am sure that with further studies this method will prove to be a very adequate means of controlling insufficiency of the mitral valve.

DR. JAMES H. WIBLE, Detroit: I would like to add a few points to this last paper for purposes of completeness.

In pursuing this study one of our major problems was making mitral insufficiency in animals which was comparable to that in humans and at the same time compatible with life. We tried many methods and finally evolved one which seemed to us, at least, to work pretty well.

[Slide] In this slide you can see the method we used. The trocar is quite similar to the one used for introducing the valve. The trocar is introduced in a similar manner, except that it is inserted through the posterior leaflet. This gives a good jet of insufficiency, and this insufficiency can be verified by direct pressure recordings from the left auricle.

Elgiloy, which is the metal used in the prosthesis, is an alloy composed of many different elements—cobalt, manganese, chromium, and so on, and very little iron. It has several interesting properties which make it useful for our purpose. It can be shaped while in a soft, easily workable state, and, then, by a simple heat process it can be converted into a long-lasting spring.

The Elgin people have assured us that Elgiloy, used in this motion, should have an infinite life, and then, upon defining what they considered "infinite life," they considered 300 years as a rather conservative estimate.

Another consideration is this: We have considered the possibility of inserting a similar type of spring prosthesis at the aortic annulus for the control of aortic insufficiency. We feel this is technically feasible and might be a bit better approach to that problem.

REFERENCES

1. Bailey, C. P.: The Surgical Treatment of Mitral Stenosis, Dis. Chest. **15**:377, 1949.

2. Bailey, C. P.; O'Neill, T. J. E.; Glover, R. P.; Jamison, W. L., and Redondo-Ramirez, H. P.: Surgical Repair of Mitral Insufficiency (Preliminary Report), Dis. Chest **19**:125, 1951.

3. Moore, T. C., and Shumacker, H. B.: Unsuitability of Transventricular Autogenous Slings for Diminishing Valvular Insufficiency, Surgery **33**: 173, 1953.

4. Harken, D. E.; Black, H.; Dexter, L.; Ellis, L. B., and Ottosen, P.: The Surgical Correction of Mitral Insufficiency, S. Forum, **39**:4, 1953.

5. Bailey, C. P.; Bolton, H. E., and Redondo-Ramirez, H. P.: Surgery of the Mitral Valve, S. Clin. North America **32**:1807, 1952.

6. Denton, G. R.: A Plastic Prosthesis (Without Moving Parts) for the Atrio-Ventricular Valve, read at Clinical Sessions of the American College of Surgeons, Oct. 23, 1953.

7. Davila, J. C.; Mattson, W. W., Jr.; O'Neill, T. J. E., and Glover, R. P.: A Method for Surgical Correction of Mitral Insufficiency: 1. Preliminary Consideration, Surg., Gynec. & Obst. **98**:407, 1954.

8. Hurwitt, E. S.; Hoffert, P. W., and Ferreira, F.: The Experimental Production and Correction of Mitral Insufficiency, Surgery **37**:15, 1955.

9. Murray, G.; Wilkinson, F. R., and McKenzie, R.: Reconstruction of the Valves of the Heart, Canad. M. A. J. **38**:317, 1938.

10. Carter, M. G.; Gould, J. M., and Mann, F. B., Jr.: Surgical Treatment of Mitral Insufficiency, J. Thoracic Surg. **26**:572, 1953.

11. Johns, T. N. P., and Blalock, A.: Mitral Insufficiency: The Experimental Use of a Mobile Polyvinyl Sponge Prosthesis, Ann. Surg. **140**:335, 1954.